Form approved
OMB No. 0925-0001

DEPARTMENT OF HEALTH AND HU
PUBLIC HEALTH SERVI
GRANT APPLICATI
FOLLOW INSTRUCTIONS CAR

LEAVE BLANK
NAME: BRACKEN, MICHAEL B
APPL NO: ~~1 R01 HD22901-01~~
DUAL: DA
IRG: EDC 1
COUN DATE: 01/87
DATE RECD: 06/01/86
DP: FR

1. TITLE OF APPLICATION *(Do not exceed 56 typewriter spaces)*
ENVIRONMENTAL TOBACCO SMOKE and PREGNANCY OUTCOME

2. RESPONSE TO SPECIFIC PROGRAM ANNOUNCEMENT ☒ NO ☐ YES *(If "YES," state RFA number and/or announcement title)*

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME *(Last, first, middle)*
Bracken, Michael B.

3b. SOCIAL SECURITY NUMBER

3c. POSITION TITLE
Professor

3d. MAILING ADDRESS *(Street, city, state, zip code)*
Dept. Epidemiology & Public Health
Yale Medical School
60 College Street
New Haven, CT 06510

3e. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT
Epidemiology and Public Health

3f. MAJOR SUBDIVISION
School of Medicine

3g. TELEPHONE *(Area code, number and extension)*
(203) 785-2846

4. HUMAN SUBJECTS
☐ NO ☒ YES ☐ Exemption # _____ OR ☒ Form HHS 596 enclosed

5. RECOMBINANT DNA
☒ NO ☐ YES

6. DATES OF ENTIRE PROPOSED PROJECT PERIOD
From: July 1st, 1987 Through: Dec 31st, 1991

7. DIRECT COSTS REQUESTED FOR FIRST 12-MONTH BUDGET PERIOD *(from page 4)*
$ 291,805

8. DIRECT COSTS REQUESTED FOR ENTIRE PROPOSED PROJECT PERIOD *(from page 5)*
$ 1,836,670

9. PERFORMANCE SITES *(Organizations and addresses)*
Yale Perinatal Epidemiology Unit
874 Howard Avenue
New Haven, Conn. 06510

Yale-New Haven Hospital
20 York Street
New Haven, Conn. 06510

10. INVENTIONS *(Competing continuation application only)*
☒ NO ☐ YES ☐ Previously reported OR ☐ Not previously reported

11. APPLICANT ORGANIZATION *(Name, address, and congressional district)*
Yale University
155 Whitney Avenue
New Haven, Conn. 06520

3rd Congressional District

12. TYPE OF ORGANIZATION
☐ Public. Specify ☐ Federal ☐ State ☐ Local
☒ Private Nonprofit
☐ For Profit *(General)*
☐ For Profit *(Small Business)*

13. ENTITY IDENTIFICATION NUMBER
1060646973A1

14. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR BIOMEDICAL RESEARCH SUPPORT GRANT
Code 13 Description School of Public Health

15. OFFICIAL IN BUSINESS OFFICE TO BE NOTIFIED IF AN AWARD IS MADE *(Name, title, address and telephone number.)*
H. G. Aaslestad, Ph.D., Director
Grant & Contract Admin
School of Medicine
333 Cedar Street
New Haven, CT 06510
(203) 785-4689

16. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION *(Name, title, address and telephone number)*
Verna M. Lingis, Assoc. Dir
Grant & Contract Adm.
School of Medicine
333 Cedar Street
New Haven, CT 06510
(203) 785-4689

17. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense *(U.S. Code, Title 18, Section 1001)*.

SIGNATURE OF PERSON NAMED IN 3a *(In ink. "Per" signature not acceptable)*
[signature]
DATE 5-27-86

18. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense *(U.S. Code, Title 18, Section 1001)*.

SIGNATURE OF PERSON NAMED IN 16 *(In ink. "Per" signature not acceptable)*
Verna M. Lingis
DATE 5/30/86

PHS 398 (Rev. 5/82)

2023488409

OTHER SUPPORT

(Use continuation pages if necessary)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications and proposals pending review or funding; (3) applications and proposals planned or being prepared for submission. Include *all* Federal, non-Federal, and institutional grant and contract support. If none, state "none." For each item give the source of support, identifying number, project title, name of principal investigator/program director, time or percent of effort on the project by professional named, annual direct costs, and entire period of support. (If part of a larger project, provide the titles of both the parent project and the subproject and give the annual direct costs for each.) Describe the contents of each item listed. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, delineate and justify the nature and extent of the scientific and budgetary overlaps or boundaries.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: Michael B. Bracken

(1) ACTIVE SUPPORT:

N515978-07 National Acute Spinal Cord Injury Study, P.I., M.B.Bracken, 25%, 8/1/84 to 7/31/88 - $396,427.

HD 16282-03 Environmental Risk Factors Related to Male Subfertility, P.I., M.B.Bracken, 25%, $169,659, 7/1/83 to 6/30/87.

(2) PENDING:

Long-Term Effects of Antenatal Exposure to Ultrasound, P.I., D.T.Scott, 10% $190,416 - 12/1/86 to 11/30/91.

(1) ACTIVE SUPPORT: Theodore R. Holford

51103
CA00875-03 Preventive Oncology Academic Award, P.I., George Roush, 30%, 8/1/83 - 7/31/88 - $70,424.

51638
CA30931-05A1 Systematic Analysis Connecticut Cancer Incidence Trends, P.I. Theodore Holford, 20%, 8/1/81 - 11/30/88 - $95,129.

51192
5RO1 HD 16282-03 Environmental Risk Factors Related to Male Subfertility, P.I., M.B.Bracken, 10%, 7/1/83 - 6/30/87, $169,659.

51932
1RO1 CA39477-01 An Epidemiologic Study of Multiple Primary Breast Cancer, P.I., W. Douglas Thompson, 10%, 4/1/85 - 3/31/88 - $176,161.

51152
5T32CA09279-08 Cancer Epidemiology and Biostatistics, P.I., Theodore Holford, 20%, 9/1/83 - 8/31/88 -

(1) ACTIVE SUPPORT: Kathleen Belanger

HD 16282-03 National Acute Spinal Cord Injury Study, P.I., M.B.Bracken 100%, 8/1/84 - 7/31/88 - $396,427 (1 year post doctoral research position)

(2) PENDING

Long-Term Effects of Antenatal Exposure to Ultrasound, P.I., D. T. Scott, 50%, 12/1/86 - 11/30/91.

Pulsed Doppler Studies of Normal and IUGR Fetuses, P.I., J.A.Copel, 20%, 7/1/87 - 6/30/92.

OTHER SUPPORT

(Use continuation pages if necessary)

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PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:

(1) ACTIVE SUPPORT: (Dr. Brian Leaderer)

NIH Grant ES 00354: "Human Responses to the Indoor Environment"; P.I. J.A.J. Stolwijk; Percent of Effort, Dr. Leaderer 80%; Annual Direct Costs $506,586 (7/1/84 - 6/30/86); Project Direct Costs $1,696,900 (7/1/82 - 6/30/86).

EPA Gas Research Institute: "Characterization of Indoor Sources of Air Contaminants"; P.I. Dr. Brian Leaderer; Percent of Effort 5%; Annual Direct Costs $52,650 (4/8/85 - 9/30/86); EPA Contract #CR-812389-01-0.

PROPOSALS PENDING:

American Society of Heating, Refrigerating & Air-Conditioning Engineers, Inc., (ASHRAE): "Sensory Reactions to Environmental Tobacco Smoke and Formaldehyde"; P.I. Dr. William Cain; Percent of Effort, Dr. Leaderer, 15%; Annual Direct Costs $69,527 (4/1/86-3/31/87); Project Direct Costs $144,068 (4/1/86 - 3/31/88).

2023498411

Form approved
OMB No. 0925-0001

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DEPARTMENT OF HEALTH AND HU
PUBLIC HEALTH SERVI

GRANT APPLICATI

FOLLOW INSTRUCTIONS CAR

NAME: BRACKEN, MICHAEL B
APPL NO: ~~1 R01 HD22901-01~~ / R01 DA-05434-01
DUAL: DA
IRG: EDC 1
COUN DATE: 01/87
DATE RECD: 06/01/86
DIF: FR

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Bracken, Michael B.

3b. SOCIAL SECURITY NUMBER
048-48-9024

3c. POSITION TITLE
Professor

3d. MAILING ADDRESS *(Street, city, state, zip code)*
Dept. Epidemiology & Public Health
Yale Medical School
60 College Street
New Haven, CT 06510

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SIGNATURE OF PERSON NAMED IN 16 *(In ink. "Per" signature not acceptable)*
Verna M. Lingis
DATE 5/30/86

PHS 398 (Rev. 5/82)

2023488412

ABSTRACT OF RESEARCH PLAN

PHS PROFESSIONAL PERSONNEL ENGAGED ON PROJECT

NAME		POSITION TITLE	DEPARTMENT AND ORGANIZATION
Michael B. Bracken	Ph.D.	Professor	Epidemiology, Obstetrics and Gynecology
Brian P. Leaderer	Ph.D.	Associate Professor	Epidemiology (Environmental Health) Pierce Foundation
Theodore R. Holford	Ph.D.	Associate Professor	Public Health (Biostatistics)
Kathleen Belanger	Ph.D.	Assoc. Res. Scientist	Epidemiology, Obstetrics and Gynecology

ABSTRACT OF RESEARCH PLAN State the application's long-term objectives and specific aims, making reference to the health relatedness of the project, and describe concisely the methodology for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. The abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. DO NOT EXCEED THE SPACE PROVIDED.

Unlike direct maternal cigarette smoking, which is consistently found to increase risk for intrauterine growth retardation (IUGR), the effect of environmental tobacco smoke upon the fetuses of mothers who do not themselves smoke is unknown. According to preliminary data of our own as many as 24% of all pregnant women may be exposed to environmental smoke while not smoking themselves and even modest risks would affect many neonates. Additionally, misclassification of "passive" smokers as "unexposed" may have seriously underestimated the health effects of direct smoking.

This study tests the hypothesis that environmental tobacco smoke is associated with an increased risk of IUGR. This association will be evaluated for evidence of a dose relation, for interactive effects between environmental smoke exposure and other known risk factors for IUGR, and for different effects of exposure throughout pregnancy.

To evaluate the validity of different measures of environmental smoke exposure, a nested study design is used. Data are collected by questionnaire, personal nicotine monitors, and urinary cotinine, a biochemical marker of exposure. A purposeful sample (n=300) will be used to quantitate environmental tobacco smoke at home, and to study fetal exposure by measuring continine in amniotic fluid and cord blood.

Detailed questions will also be asked about maternal marijuana use throughout pregnancy to test a hypothesis that such use is also related to increased risk of IUGR in offspring. Some of each maternal urine sample will be stored for later testing for Δ 9 - THC metabolites, a market for marijuana use (funding for which is not requested at present).

A total of 4000 women will be enrolled into this prospective study at their first antenatal visit and followed prospectively throughout pregnancy. IUGR will be evaluated using the 5th and 10th percentiles of weight for gestational age and the Ballad neurological and morphologic examination of the neonate.

This study will provide important methodological correlations of environmental smoke as assessed by questionnaire, aerometric measures and biochemical markers. Evidence for an effect of environmental smoke on perinatal outcomes will have important implications for public health policy.

VERTEBRATE ANIMALS INVOLVED ☒ NO ☐ YES If "YES," identify by common names and underline primates

TABLE OF CONTENTS

Number pages consecutively at the bottom throughout the application. Do not use suffixes such as 5a, 5b. Type the name of the Principal Investigator, Program Director at the top of each printed page and each continuation page.

SECTION 1.

SECTION 2.

SECTION 3. Appendix *(Six sets) (No page numbering necessary for Appendix)*

Number of publications: _____ Number of manuscripts: _____

Other items (list):

Appendices A, B, C, D.

Three letters

Application Receipt Record, form PHS 3830
Form HHS 596 if Item 4, page 1, is checked

20234884

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR — Michael B. Bracken

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM 7/1/87 THROUGH 6/30/88

DOLLAR AMOUNT REQUESTED (Omit cents)

PERSONNEL (Applicant organization only)		TIME/EFFORT				
NAME	POSITION TITLE	%	Hours per Week	SALARY	FRINGE BENEFITS **	TOTALS
M. Bracken	Principal Investigator	30				
T. Holford	Co-Investigator	10				
K. Belanger	Project Director	80				
# J-e McSharry	Project Coordinator	80				
# K. Hellenbrand	Data Manager	60				
# K. Hauser	Assoc in Research	100				
# T-B-N 6 positions*	Asst. in Research	100				
# T-B-N (6 mos)	Computer Operator	50				
# Wanda Carr (6 mos)	Coder	100				
# L. Mann	Secretary	100				
	SUBTOTALS →					

REDACTED

CONSULTANT COSTS

* In the first year six research assistants to be hired for 6,5,4,3,2 and 1 month

** 30% TIA, 28.5% non-TIA

EQUIPMENT (Itemize)

(see attached sheets for details) Computer 9,799

9,799

SUPPLIES (Itemize by category)

(see Other Expenses)

TRAVEL	DOMESTIC	6,912
	FOREIGN	
PATIENT CARE COSTS	INPATIENT	
	OUTPATIENT	

ALTERATIONS AND RENOVATIONS (Itemize by category)

CONSORTIUM/CONTRACTUAL COSTS

Sub-contract with Pierce Foundation Laboratory 47,529

OTHER EXPENSES (Itemize by category)

(see attached sheets for details) 26,85(

Revised budget for #230234 submitted in Verna Lesia's letter of 7/20/87 to Pat

TOTAL DIRECT COSTS (Also enter on page 1, item 7) → $ 291,805

20234 8415

PHS 398 (Rev. 5/82) PAGE 4

#Personnel in off-campus facility (Indirect Costs 43.9% MTDC per DHHS agreement dated 6/7/85.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR Michael B. Bracken

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS		1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED 2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)		REDACTED				
CONSULTANT COSTS						
EQUIPMENT		9,799	-0-	-0-	-0-	-0-
SUPPLIES		-0-	-0-	-0-	-0-	-0-
TRAVEL	DOMESTIC	6,912	19,501	21,083	8,344	1,021
	FOREIGN					
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT					
ALTERATIONS AND RENOVATIONS						
CONSORTIUM/ CONTRACTUAL COSTS (OH)		32,898 14,631	75,584 19,598	77,749 20,774	54,222 20,182	11,792 6,800
OTHER EXPENSES		26,855	35,695	37,862	38,131	20,930
TOTAL DIRECT COSTS		291,805	475,848	517,576	424,295	127,146

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 8) → $ 1,836,670

JUSTIFICATION (Use continuation pages if necessary). Describe the specific functions of the personnel and consultants. If a recurring annual increase in personnel costs is anticipated, give the percentage. For *all* years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and consortium/contractual costs. For any additional years of support requested, justify any significant increases in any category over the first 12 month budget period. In addition, for COMPETING CONTINUATION applications, justify any significant increases over the current level of support.

See page for budget justification.

Michael B. Bracken

Year 1

Personnel:		REDACTED
Equipment:		
2 IBM XT personal computers	4,768	
1 IBM At personal computers	4,169	
11 NEC Spinwriter 3550 printer	862	9,799
Domestic Travel:		
To collect samples	1,700	
Initial interviews	4,462	
1 conference for one investigator	750	6,912
Sub contract:		47,529*
Other:		
2 file cabinets	700	
1 small Refrigerator/Freezer	200	
Tape, diskettes, paper for printer	200	
Statistical software license	500*	
Gandalf communications line @ 100/month	1,200	
Telephone 12 months @ 100/month	1,200	
Postage	350	
Office supplies	1,080	
Printing:		
Screening cards (5000)	325	
Initial interviews (4000)	1,925	
Telephone questionnaires (6000)	175	
Computer mainframe	10,000*	
Office rental	9,000*	26,855
	Total	291,805

* Not subject to indirect costs

Year 2 (July 1, 1988 - June 30, 1989)

Personnel	%
M. Bracken	30
T. Holford	10
K. Belanger	80
# J-e McSharry	80
# K. Hellenbrand	60
# K. Houser	100
# Assts in Res. (12 mo) 5 -	100
(12mo) 1 -	50
# Computer Operator	50
# Coder/data entry	100
# Secretary	100

REDACTED

REDACTED

8% salary and fringe increase over Year 1

#Personnel located in off-campus facility

Michael B. Bracken

Year 2

Personnel		REDACTED
Domestic travel:		
Collect samples	8,187	
Initial interviews	8,237	
Post partum interviews (30%)	2,267	
1 Conference Investigator (8% increase over Year 1)	810	19,501
Sub contract		95,182*
Other:		
Tape, diskettes, paper for printer	216	
Statistical software license	540	
Gandalf communications line @ 108/month	1,296	
Telephone	1,296	
Postage	500	
Office supplies	1,165	
Printing:		
post partum questionnaire (4000)	1,100	
medical records review forms (4000)	350	
Computer mainframe	18,000*	
Misc. office equipment (4 file cabinets - 4 drawers @ 378 each)	1,512	
Office rental	9,720*	35,695
	Total	475,848

*Not subject to indirect costsrate

Year 3 (July 1, 1989 - June 30, 1990)

Personnel

		%
	M. Bracken	30
	T. Holford	20
	K. Belanger	80
#	J-e McSharry	80
#	K. Hellenbrand	60
#	K. Houser	100
#	Assts in Res.(12 mo)5 -	100
	(12 mo) 1 -	50
#	Computer Operator	50
#	Coder/data entry	100
#	Secretary	100

REDACTED

REDACTED

8% salary and fringe increase over Year 2

Personnel located in off-campus facility

Michael B. Bracken

Year 3

REDACTED

Personnel		
Domestic travel:		
To collect samples	8,842	
Initial Interviews	8,896	
Post partum interviews (30%)	2,470	
1 Conference for investigator	875	21,083
Sub contract:		98,523*
Other:		
Misc. office equipment (4 file cabinets - 4 drawers) @ 408 ea.	1,632	
Tape, diskettes, printer ribbon	233	
Statistical software license	583*	
Gandalf communications line @ 117/month	1,400	
Telephone	1,400	
Postage	540	
Office supplies	1,258	
Printing forms	378	
Computer mainframe	19,940*	
Office rental	10,498*	37,862
	Total	517,576

* Not subject to indirect costs

Year 4 (July 1, 1990 - June 30, 1991

	Personnel	%
	M. Bracken	30
	T. Holford	20
	K. Belanger	80
#	J-e McSharry	80
#	K. Hellenbrand	60
#	K. Houser	100
#	Assts in Res.*	100
#	Computer Operator	50
#	Coder/data entry	100
#	Secretary	100

REDACTED

8% salary and fringe increase over Year 3

* 5 Research Assistants only - 100% - 1 each for 8 months, 7 months, 6 months, 5 months, 4 months

#Personnel located in off-campus facility

Michael B. Bracken

Year 4

Personnel		REDACTED
Domestic travel:		
To collect samples	3,848	
Initial interviews	1,544	
Post partum interviews	2,007	
1 conference for investigator	945	8,344
Sub contract:		74,404*
Other:		
Misc. office equipment (4 file cabinets - 4 drawers) @ 441 ea.	1,764	
Tape, diskettes, printing paper	252	
Statistical software license	630*	
Gandolf communications line @ 126/month	1,512	
Telephone	1,512	
Postage	400	
Office supplies	700	
Computer mainframe	21,535*	
Office rental	11,338*	38,131
	Total	424,295

* Not subject to indirect costs

Year 5 (July 1, 1991 - December 31, 1991)

Personnel	%
M. Bracken	30
T. Holford	20
K. Belanger	80
# J-e McSharry	80
# K. Hellenbrand	60
# Secretary	100

REDACTED

#Personnel located in off-campus facility

Michael B. Bracken

Year 5

Personnel		REDACTED
Domestic travel:		
1 conference for an investigator		1,021
Sub contract		18,592 *
Other:		
Misc. office equipment		
1 file cabinet - 4 drawers) @ 476 ea.	476	
Tape diskettes, printer ribbons, paper	136	
Statistical software license	340*	
Gandalf communications line @ 136/month	816	
Telephone	816	
Postage	216	
Office supplies	378	
Computer mainframe	11,629*	
Office rental	6,123*	20,930
	Total	127,146

* Not subject to indirect costs

JOHN B. PIERCE FOUNDATION
LABORATORY, INC
290 CONGRESS AVENUE
NEW HAVEN, CONNECTICUT 06519

ASSISTANT SECRETARY AND
ASSISTANT TREASURER

REDACTED

May 22, 1986

Mr. Halber Aaslestad, Director
Grant & Contract Administration
School of Medicine (I203SHM)
333 Cedar Street
New Haven, CT 06510

Dear Mr. Aaslestad:

This letter is to confirm The John B. Pierce Foundation Laboratory's commitment on behalf of Dr. Brian Leaderer to participate with Dr. Michael Bracken in "Environmental Tobacco Smoke and Perinatal Outcomes" for the period 7/1/87 - 12/31/91, which I understand will be submitted by the Yale University School of Medicine to the National Institutes of Health.

Enclosed is our budget presentation which provides a first year through five year summary in accordance with the usual NIH/PHS 398 format. Our proposed total direct and indirect costs are $47,529 for the first year, $95,182 for the second year, $98,523 for the third year, $74,404 for the fourth year, and $18,592 for the fifth year. The five-year total of direct and indirect costs is $334,230.

Sincerely,

Joel A. Wasserman
Assistant Treasurer

Encs.
JAW:mmm

cc: Dr. Bracken
Dr. Leaderer

2023488426

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD DIRECT COSTS ONLY

FROM 7/1/87 THROUGH 12/31/91

DOLLAR AMOUNT REQUESTED (Omit cents)

PERSONNEL (Applicant organization only) NAME	POSITION TITLE	TIME/EFFORT %	Hours per Week	SALARY	FRINGE BENEFITS	TOTALS
Leaderer, B.P.	Principal Investigator	30		REDACTED		
Tosun, T.	Research Associate	25				
SUBTOTALS →				REDACTED		

CONSULTANT COSTS

EQUIPMENT (Itemize)

1 Freezer (for storing specimens)	1,200	
10 Ice chests (to transport specimens) @ 35.00 ea.	350	
A)Construction of Passive Monitors for Nicotine		1,550

SUPPLIES (Itemize by category)

1) Plastic cassettes	1,000	
2) Nucleopore filters	800	
3) Millipore filters	400	
4) Support filters	400	
5) Chemicals	75	
B) Collection of cotinine samples - specimen containers	500	3,175

TRAVEL	DOMESTIC	
	FOREIGN	
PATIENT CARE COSTS	INPATIENT	
	OUTPATIENT	

ALTERATIONS AND RENOVATIONS (Itemize by category)

CONSORTIUM/CONTRACTUAL COSTS

Cotinine/creatinine analysis will be done by the American Health Foundation (see attached letter from Dr. Haley) 58 urine samples @$15/sample	870	
58 amniotic fluid samples @ $15/sample	870	
Number of samples includes 5% increase for Quality Control		1,740

OTHER EXPENSES (Itemize by category)

Analysis of Passive Monitors for nicotine at Pierce Laboratory		
58 personal samples @ $25/sample	1,450	
15 house samples @ $25/sample	375	
Number of samples includes 5% increase for Quality Control		1,825
TOTAL DIRECT COSTS (Also enter on page 1, item 7)		32,898
Indirect Costs at 76.4% S&W (19,150) →		$ 14,631
TOTAL		$ 47,529

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PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS		1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED 2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits) (Applicant organization only)		REDACTED				
CONSULTANT COSTS		-	-	-	-	-
EQUIPMENT		1,550	-	-	-	-
SUPPLIES		3,175	1,850	1,750	1,050	-
TRAVEL	DOMESTIC	-	-	-	-	-
	FOREIGN					
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT					
ALTERATIONS AND RENOVATIONS						
CONSORTIUM/ CONTRACTUAL COSTS		1,740	16,815	16,815	7,260	-
OTHER EXPENSES		1,825	23,700	23,700	11,175	REDACTED
TOTAL DIRECT COSTS		32,898	75,584	77,749	54,222	
Indirect Costs 76.4%		14,631	19,598	20,774	20,182	6,800
TOTAL		47,529	95,182	98,523	74,404	18,592
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 8) →					TOTAL	$ Total Dir. 252,245 Total I.C. 81,985 334,230

JUSTIFICATION (Use continuation pages if necessary): Describe the specific functions of the personnel and consultants. If a recurring annual increase in personnel costs is anticipated, give the percentage. For *all* years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and consortium/contractual costs. For any additional years of support requested, justify any significant increases in any category over the first 12 month budget period. In addition, for COMPETING CONTINUATION applications, justify any significant increases over the current level of support.

2nd Year:

A) Personnel
1. 6% Salary increase
2. Tosun, T. - increase effort to 50%
3. Fringe rate of 29.5%

B) Supplies
1. Air Monitors
   a) Nucleopore filters - $300
   b) Millipore filters - 400
   c) Support pads - 400
   d) Chemicals - 50
2. Specimen Containers - 700

(SEE NEXT PAGE)

2nd Year (Continued):

C) Consortium/Contractual Costs

1. Cotinine/creatinine analysis will be done by the American Health Foundation (see attached letter from Dr. Haley)

a) Urine samples, 827 @ $15/sample	$12,405
b) Amniotic fluid, 126 @ $15/sample	1,890
c) Cord blood, 168 @ $15/sample	2,520

Number of samples includes 5% increase for Quality Control

D) Other Expenses

Analysis of Passive Monitors for nicotine will be done at the Pierce Laboratory

a) Personal samples, 827 @ $25/sample	$20,675
b) House samples, 121 @ $25/sample	3,025

Number of samples includes 5% increase for Quality Control

3rd Year:

A) Personnel

1. 6% Salary increase
2. Fringe rate @ 30.5%

B) Supplies

1. Air Monitors	
a) Millipore filters	$600
b) Support pads	400
c) Chemicals	50
2. Specimen containers	700

C) Consortium/Contractual Costs

1. Cotinine/creatinine analysis will be done by the American Health Foundation (See attached letter from Dr. Haley)

a) Urine samples, 827 @ $15/sample	$12,405
b) Amniotic fluid , 126 @ $15/sample	1,890
c) Cord blood, 168 @ $15/sample	2,520

Number of samples includes 5% increase for Quality Control

D. Other Expenses

Analysis of Passive Monitors for nicotine will be done at the Pierce Laboratory

a) Personal samples, 827 @ $25/sample	20,675
b) House samples 121 @ $25/sample	3,025

Number of samples includes 5% increase for Quality Control

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4th Year:

A) Personnel

1. 6% Salary increase
2. Fringe rate @ 31.5%
3. Tosun, T. - reduce effort to 40%

B) Supplies

1. Air Monitors
   a) Millipore filters 400
   b) Support pads 200
   c) Chemicals 50
2. Specimen containers 400

C) Consortium/Contractual Costs

1. Cotinine/creatinine analysis will be done by the American Health Foundation (See attached letter from Dr. Haley)

   a) Urine samples , 389 @ $15/sample $5,835
   b) Amniotic fluid , 32 @ $15/sample 480
   c) Cord blood , 63 @ $15/sample 945

   Number of samples includes 5% increase for Quality Control

D) Other Expenses

Analysis of Passive Monitors for nicotine will be done at the Pierce Laboratory

   a) Personal samples , 389 @ $25/sample $9,725
   b) House samples , 38 @ $25/sample 1,450

   Number of samples includes 5% increase for Quality Control

5th Year - 1/2 Year:

A) Personnel

1. 6% salary increase
2. Fringe rate @ 32.5%
3. Tosun, T. - reduce effort to 0%

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Budget Justification

Personnel

Dr. Bracken will have overall resposibility for the project and will be actively involved with recruitment of staff, major aspects of the study design, data analysis and report writing. Dr. Bracken is Director of the Yale Perinatal Epidemiology Unit within which the project will be housed. He has directed many prior studies of environmental risk factors for intrauterine growth retardation, as well as other perinatal outcomes, including the previous Yale study of passive smoke exposure and low birthweight.

Dr Leaderer will be responsible for all biochemical and environmental monitoring aspects of the study. He directs an extensive program to develop and evaluate methods for assessing air quality and serves on the National Academy of Sciences Committee on Passive Smoking.

Dr. Holford will be responsible for the data analysis in this project and will advise on data management and research design issues. He has worked previously with Dr. Bracken in the perinatal epidemiology studies and with Dr. Leaderer on environmental monitoring and air quality studies. Dr. Holford has also made independent contibutions to the development of new methods of mutivariable analysis for epidemiologic studies.

Dr. Belanger will direct and be involved with all aspects of the project; particularly the design of data collection instruments, study protocols, contacts with private obstetrrical practices, training and supervision of project personnel, overseeing data collection, data management, collaboration on data analysis and report writing. She will provide daily expertise to the scientific conduct of the project and will be directly responsible for recruitment and training of research staff. Dr. Belanger's pre and postdoctoral training was in perinatal epidemiology at Yale.

Jean-ellen McSharry will be responsible for the daily data collection procedures. She will establish, under Dr. Belanger's supervision, the mechanisms for identifying study subjects, introducing the study to them and accomplishing the complex data collection procedures required by the study protocol. Ms. McSharry has been a project coordinator and research assistant at the Yale Perinatal Epidemiology Unit for several years.

Karen Hellenbrand is the senior systems programmer/analyst in the Yale Perinatal Epidemiology Unit and she will be responsible for developing the data management and analysis systems that a study of this complexity demands. Ms. Hellenbrand will be responsible for generating routine data reports, as well as writing and running the data analysis programs. Additionally, she will execute the sampling design. This includes not only assigning women to specific groups but also tracking them though pregnancy to insure that they will be monitored at the correct time intervals.

One part time (50 per cent) computer operator will be hired to assist with the more routine aspects of the data management component of the study. This individual will work under the direct supervision of Ms. Hellenbrand, freeing her for the more demanding technical tasks of data analyses. A coder data entry person will be required on a full time basis from the beginning of the pilot study (1/1/88) until the end of the data clean-up (6/30/91). In this study it is essential that the data, from the initial interview, be entered on-line as quickly as possible since this information will be used to randomize women into groups for monitoring.

To determine the number of research assistants that will be needed, the data collection phase of the study was broken down into individual tasks. Each task was assigned an estimated time for completion based on consultations with experienced field interviewers and supervisors at the Yale Perinatal Epidemiology Unit. The following estimates were derived:

Initial Interview	2.0 hours
Amniocentesis contact and follow-up	1.5 hours
Biochemical monitoring	2.5 hours
Telephone questionnaire	.5 hours
Post-partum questionnaire	1.5 hours
Medical records review	.5 hours

These estimates include travel time and the time to contact patients to arrange interviews and monitoring visits. To arrive at the number of man-hours needed each week, each task was multiplied by the number of times it would be done per week. An estimate of 33 new patients entering the study per week was used in these calculations. During the first seven months of data collection the number of man hours per week will gradually increase from 66 hours (33 interviews) to 192.5 man hours (33 interviews, 16.3 biochemical monitoring visits, 3 amniocenteses, 30 telephone questionnaires, 33 post partum questionnaires, 33 medical record reviews). To accommodate this gradually increasing workload, research assistants will be hired and trained as needed during the first year of the study. A similar procedure will be followed in the fourth year of the study. When new patients cease to be enrolled, the work load will decrease gradually and research assistants will be released gradually from the project.

Personnel costs for Year 2 - Year 5 include increases of 8 per cent to cover increases in both salary and fringe benefits for staff and professional personnel.

Computer Equipment

There are two major components to the computer costs in a study of this size, data management and analysis. The data management phase includes entering the data, error checking and making corrections, and linking data entered at different points in time for the same study patient. The analysis phase includes linking information from different computer files and performing statistical analyses. To reduce costs in the data management phase, two IBM personal computers will be used. The IBM XT will be used to enter all of the data, make error checks and corrections and transmit the data to the mainframe computer at Yale Computer Center. The IBM AT will be used, simultaneously, by the systems programmer to develop data management programs, to manipulate files, to

perform preliminary analysis, and to store data from the shorter forms. The longer forms (initial interviews and medical record reviews) will be entered and corrected on the personal computer, but will be transmitted to the mainframe for storage on tape. This is due to the inherent limitations in the number of variables that can be handled by the personal computer.

Two Gandalf lines will be installed for data transmission between Yale Computer Center and the Yale Perinatal Epidemiology Unit. They are required to upload and download files between the personal computers and the mainframe. In addition, they will save time by permitting the staff to conduct all data management functions at the Perinatal Epidemiology Unit, without frequent trips to Yale Computer Center.

The Statistical Analysis System (SAS) will be used for all data file creations and editing as well as producing weekly reports and performing statistical analyses. This will require a software license to run SAS on the personal computer. However, by using SAS for both the mainframe and personal computers, minimal file reformatting and changes will be necessary to combine information for analysis.

The second IBM XT personal computer will be used as a dedicated word processing machine; to design all of the forms used in the study, to send introductory letters to all study participants and to prepare reports for publication. A letter quality printer will also be needed.

Domestic Travel

Travel expenses have been estimated at the current Yale rate of twenty cents per mile and an estimated round trip of 26 miles ($5.20 per trip). Each reseach assistant will be assigned to a specific geographic area, this will reduce both the travel expense for milage and also the travel time. However, this study will involve extensive travel. Research assistants will be required to visit each study participant once to obtain the initial interview. Two visits will be required each time a woman is monitored and approximately 30 percent of study patients will be visited at home to conduct the post partum interview.

Travel expense for one investigator to attend one scientific meeting per year has also been included, with annual increases of 8 percent.

Other Expenses

Over the four and one-half years of the study, 15 four drawer file cabinets with locks will be purchased. They will be used for the proper storage of study forms. Each study participant will have an initial interview, postpartum interview, telephone questionnaire and medical records review form. Women in the monitored group will have several additional forms.

One small refrigerator/freezer will be used at the Perinatal Epidemiology Unit for the temporary storage of specimens. This is to prevent deterioration of specimens and ensure accurate measurement of cotinine levels. Specimens will be transferred to the Pierce Foundation laboratory for long term storage.

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Telephone charges have been estimated at $100 per month with annual increases of 8 per cent. This includes the cost of three telephone lines at the Perinatal Epidemiology Unit and long distance charges to contact women living outside the New Haven local calling area. Telephone communication will be vital in this study. Each of the 4000 participants will be contacted by phone to arrange an initial interview; 3700 women will receive a telephone interview during the course of the study; 2000 women will be contacted by phone to arrange appointments for personal monitors; 400 women will be contacted to arrange procedures for collecting amniotic fluid; 1200 women will be contacted after delivery for postpartum interviews at home.

Postage has been estimated to include the following costs: mailing 5,000 introductory letters to women potentially eligible to participate; sending letters to women who cannot be contacted by telephone to arrange interviews and monitoring; general correpondence.

This study will require printing the following forms: 5,000 screening cards to record potentially eligible patients; 4,000 initial interview forms; 6,100 short questionnaire forms (3,700 for telephone interviews, 2,000 for monitoring, 400 with amniotic fluid samples); 4,000 post partum questionnaires; and 4,000 medical record review forms.

Office supplies includes the costs of stationary and envelopes for the 5,000 introductory letters, file folders to organize several forms for each study participant, copy charges, and general supplies for a staff of 10-12 employees.

Although personal computers will be used to their maximum capacity, the large amount of data to be processed, monitored and analyzed, requires use of the mainframe computer at Yale Computer Center. Storage costs for this large database will be minimized by storing the corrected data on tape, and complex analyses will be conducted in off-peak hours.

The Perinatal Epidemiology Unit is housed in rental space next to the hospital (as are many specialized research groups at Yale because of the shortage of on-campus space). The modified over-head for personnel in such space, however, results in a net saving of costs.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Michael B. Bracken	Professor	

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
University of London, England	B.Sc	1968	Zoology
Yale University	M.P.H.	1970	Public Health
	M.Phil	1971	Epidemiology
	Ph.D.	1974	Epidemiology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. **DO NOT EXCEED TWO PAGES.**

Employment

Professor, Epidemiology, Obstetrics and Gynecology, Yale University, 1986-.
Associate Professor, Epidemiology, Obstetrics and Gynecology, Yale University, 1983-86.
Senior Research Associate Lecturer, Epidemiology, Obstetrics & Gynecology, Yale University, 1980-83.
Director, Yale Perinatal Epidemiology Unit, 1979-.
Research Associate & Lecturer, Epidemiology, Obstetrics & Gynecology, 1973-80.

Honors

Fellow, American College of Epidemiology, 1981.

Publications: (1984 - present, from a total of 90+ refereed articles)

Bracken MB, Collins WF, Freeman DH, Shepard MJ, et al: Efficacy of methylpredisolone in acute spinal cord injury: A multicenter randomized trial. JAMA, 251:45-52, 1984.

Bracken MB, Brinton LA, Hayashi K: Epidemiology of hydatidiform mole and choriocarcinoma. Epidemiol Rev, 6: 52-75, 1984.

Jeanty P, Cousaert E, Hobbins JC, Bracken MB, Cantraine F: A longitudinal study of fetal head biometry. Am J Perinatol, 1: 118-128, 1984.

Hayashi K, Bracken MB: The epidemiology of hydatidiform mole, in M.B. Bracken, (ed) Perinatal Epidemiology, New York, Oxford University Press, 1984, 325-328.

Bracken MB: Design and conduct of randomized clinical trials in perinatal research in Perinatal Epidemiology, ibid, 397-422.

Bracken MB: Methodologic issues in the epidemiologic investigation of drug-induced congenital malformations Perinatal Epidemiology, ibid. 423-449.

Romero R, Jeanty P, Reece EA, Grannum P, Bracken MB, Holford TR, Berkowitz R, Hobbins JC: Sonographically monitored amniocentesis: a technique to decrease the incidence of intraoperative complications. Obstet Gynecol, 65: 426-430, 1985.

Bracken MB: Spermicidal contraceptives and poor reproductive outcomes: the epidemiologic evidence against an association. Am J Obstet Gynecol, 151: 552-556, 1985.

Moya F, Grannum P, Pinto K, Bracken MB, Hobbins JC, Kadar N. The ultrasound assessment of the post dates pregnancy. Obstet Gynecol, 65: 319-322, 1985.

Bracken MB: Incidence and etiology of hydatidiform mole: an epidemiologic review. JNCI In Press.

Bracken MB, Shepard MJ, Hellenbrand KG, Collins WF, et al. Methylprednisolone and neurologic function one year after injury: results of the national acute spinal cord injury study. J Neurosurg, 63: 704-713, 1985.

Eskenazi B, Bracken MB: Pyloric Stenosis and Antihistamines, Am J Epidemiol, 122: 196-197, 1985.

Bracken MB, Bryce-Buchanan C, Silten R, Holford TR. Menarcheal age and habitual miscarriage: evidence for an association. Ann Hum Biol, 12:525-531, 1985.

Bracken MB, Hellenbrand K, Holford, TR, Bryce-Buchanan C. Low birth weight after induced abortion: no evidence for an association. Am J Epidemiol, 123:604-613, 1986.

Bracken MB, Bryce-Buchanan C, Srisuphan W, Holford TR, Silten R. Risk of late first and second trimester miscarriage after induced abortion. Am J Perinatol, 3:84-91, 1986.

Srisuphan W, Bracken MB. Caffeine consumption during pregnancy and association with late miscarriage. Am J Obstet Gynecol, 154: 14-20, 1986.

Bracken MB: Drug use in pregnancy and congenital heart disease in offspring, New Engl J Med, 314: 1120, 1986.

Brinton LA, Bracken MB, Connelly RR. Choriocarcinoma incidence in the United States. Am J Epidemiol, In Press.

Martin TR, Bracken MB. Association of low birth weight with passive smoke exposure in pregnancy. Am J Epidemiol, In Press.

Shepard MJ, Hellenbrand K, Bracken MB. Proportional weight gain and complications of pregnancy, labor and delivery for healthy women of normal prepregnant stature. Am J Obstet Gynecol, In Press.

Hatch EE, Bracken MB. Association of marijuana use in pregnancy and intrauterine growth retardation. Am J Epidemiol, In Press.

Barkan S, Bracken MB. Delayed childbearing: no evidence for increased risk of low birthweight and prematurity. Am J Epidemiol, In Press.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Kathleen Pinto Belanger	Assoc. Res. Scientist	

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
College of Notre Dame of Maryland	BA	1970	Biology
University of Bridgeport, Bpt., CT	MS	1979	Biology
Yale University, New Haven, CT	Ph.D.	1985	Epidemiology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

1980 – 1982 Consultant, Statistical analysis and computer data management, Veteran's Administration Medical Center, West Haven, CT.

1982 – 1985 Project Director, Study of risk factors for female secondary infertility, Perinatal Epidemiology Unit, Yale University

1982 – Lecturer in Obstetrics and Gynecology, Yale University School of Medicine

1985 – Post doctoral Associate in Clinical Trials, Yale University School of Medicine

Publications

Moya F, Grannum P, Pinto K, Bracken MB, Hobbins JC, Kadar N. The ultrasound assessment of the post dates pregnancy. Obstetrics and Gynecology 65: 319-322, 1985.

Belanger K, Bracken MB. Induced abortion and risk of secondary infertility. American Journal of Epidemiology - submitted.

BIOGRAPHICAL SKETCH

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NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Karen G. Hellenbrand	Software Systems Programmer	

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
Smith College, Northampton, Mass.	B.A.	1976	Mathematics
Yale University, New Haven, Conn.	M.P.H.	1979	Biostatistics

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

- Assistant in Research, Yale University, Dept of Pediatric Cardiology, Summers 1971-1975, May 1976, August 1978.
- Evaluator, Family Counseling Agency of Greater New Haven, April 1978 - March 1979.
- Associate in Research, Yale University, Dept of Epidemiology and Public Health, (Biostatistics) March 1979-June 1982.
- Research Staff, Yale University, Dept of Epidemiology and Public Health, (Biostatistics) July 1982-June 1983.
- Software Systems Programmer, Yale University, Dept of Epidemiology and Public Health (Biostatistics) June 1983-

PUBLICATIONS

Bracken, Michael B., Collins, W.F., Freeman, D.F., Shepard, M.J., Wagner, F.W., Silten, R.M., Hellenbrand, K.G., Ransohoff, J., Hunt, W.E., Perot, P.L. Jr., Grossman, R.G., Green, B.A., Eisenberg, H.M., Rifkinson, N., Goodman, J.H., Meagher, J.N., Fischer, B., Clifton, G.L., Flamm, E.S., Rawe, S.E.: Efficacy of methylprednisolone in acute spinal cord injury; a multicenter randomized trial, The Journal of American Medical Association 1984, 251: 45-52.

Bracken, Michael B., Freeman, Daniel H. Jr., Hellenbrand, Karen: Hospitalization for medical-legal and other abortions in the United States, 1970-1977, The American Journal of Public Health 1982, 72: No. 1.

Bracken, Michael B., Freeman, Daniel H. Jr., Hellenbrand, Karen: Incidence of acute traumatic hospitalized spinal cord injury in the United States,1970-1977, The American Journal of Epidemiology 1981, 113: 615-622.

Bracken, Michael B., Hellenbrand, K.G., Holford, T.R., Bryce-Buchanan, C.: Low Birthweight in Pregnancies Following Induced Abortion: No Evidence for An Association, The American Journal of Epidemiology 1986, 123: 604-613.

Bracken, Michael B., Shepard, M.J., Hellenbrand, K.G., Collins, W.F., Leo, L.S., Freeman, D.H., Wagner, F.C., Flamm, E.S., Eisenberg, H.M., Goodman, J.H., Perot, P.L., Green, B.A., Grossman, R.G., Meagher, J.N., Young, W., Fischer, B., Clifton, G.L., Hunt, W.E., Rifkinsom, N.: Methylprednisolone and Neurologic Function One Year After Injury: Results of the National Acute Spinal Cord Injury Study, The Journal of Neurosurgery 1985, 63: 704-713.

Freeman, Daniel H. Jr., Hellenbrand, K., Ostfeld, A.M., D'Atri, D.A., Papke, E., Piorun, K., Richards, V.A., Sardines, A.: The prevalence distribution of hypertension: Connecticut adults 1978-1979, The Journal of Chronic Disease 1983, 36: 171-181.

Freeman, Daniel H. Jr., Ostfeld, Adrian M., Hellenbrand, Karen, Richards, Virginia A., Tracy, Robert: Changes in the Prevalence Distribution of Hypertension: Connecticut Adults 1978-1979 to 1982, The Journal of Chronic Disease 1985, 38: 157-164.

Hayashi, Kenji, Bracken, Michael B., Freeman, Daniel H. Jr., Hellenbrand, Karen: National incidence of hydatiform mole in the United States (1970-1977), The American Journal of Epidemiology 1982, 115: 67-77.

Hellenbrand, Karen, Freeman, Daniel H. Jr., D'Atri, David A.: Using boxplots in the examination of residuals, Proceedings of the American Statistical Association Meetings, 1980.

Holden, Robert A., Ostfeld, Adrian M., Freeman, Daniel H.Jr., Hellenbrand, Karen G., D'Atri, David A.: Dietary salt intake and blood pressure, The Journal of the American Medical Association 1983, 250: 365-369.

Kapp, Daniel S., Grady, Karen, Fischer, Diana, Schwarts, Peter, Second malignancies in patients with invasive carcinoma of the uterine cervix; Yale University experience, International Journal of Radiation Oncology, 1982, 8: 197-205.

Shepard, Mary J., Hellenbrand, Karen, Bracken, Michael B.: Proportional weight gain and complications of pregnancy, labor and delivery in healthy women of normal prepregnant stature, The American Journal of Obstetrics and Gynecology 1986, (in press).

Unpublished Manuscripts and Talks

Freeman, Daniel H. Jr., Hellenbrand, Karen, D'Atri, David A., Ostfeld, Adrian M., Sardinas, Anthony: Blood pressure of Connecticut adults in 1978-1979 compared to those of the United States 1971-1974, presented at the American Public Health Association, 108th Annual Meeting, October 19-23, 1980, Detroit, Michigan.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Theodore R. Holford	Associate Professor	

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
Andrews University	B.A.	1969	Math & Chem
Yale University	Ph.D.	1973	Biometry

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Positions Held:

9/72 - 12/73 Research Staff Biometrician, Yale University
1/74 - 6/79 Assistant Professor of Public Health (Biometry), Yale University
7/81 - 7/82 Sabbatical leave at the Department of Biomathematics, University of Oxford
7/84 - 6/85 Acting Head, Division of Biostatistics, Department of Epidemiology and Public Health, Yale University
7/79 - present Associate Professor of Public Health (Biostatistics), Yale University (tenure on 7/83)

Honors:

7/81 - 7/82 Recipient of an Eleanor Roosevelt International Cancer Fellowship from the UICC (International Union Against Cancer)

Selected Publications:

Holford, T.R. Life tables with concomitant information. Biometrics, 32: 587-597, 1976.

Holford, T.R., White, C. and Kelsey, J.L. Multivariate analysis for matched case-control studies. American Journal of Epidemiology, 107: 245-256, 1978.

Holford, T.R. The analysis of pair-matched case-control studies, a multivariate approach. Biometrics, 34: 665-672, 1978.

Kelsey, J.L., Dwyer, T., Holford, T.R. and Bracken, M.B. Maternal smoking and congenital malformations: An epidemiological study. Journal of Epidemiology and Community Health, 32: 102-107, 1978.

Bracken, M.B., Holford, T.R., White, C. and Kelsey, J.L. Role of oral contraception in congenital malformations of offspring. International Journal of Epidemiology, 7: 309-317, 1978.

Walter, S.D. and Holford, T.R. Additive, multiplicative, and other models for disease risks. American Journal of Epidemiology, 108: 341-346, 1978.

Bracken, M.B. and Holford, T.R. Induced abortion and congenital malformations in offspring of subsequent pregnancies. American Journal of Epidemiology, 109: 425-432, 1979.

Holford, T.R. The analysis of rates and of survivorship using log-linear models. Biometrics, 36: 299-305, 1980.

Bracken, M.B. and Holford, T.R. Exposure to prescribed drugs in pregnancy and association with congenital malformations. Obstetrics and Gynecology, 58: 336-344, 1981.

Holford, T.R. Covariance analysis for case-control studies with small blocks. Biometrics, 38: 673-683, 1982.

Holford, T.R. Strategies for the analysis of case-referent and cohort studies. In Perinatal Epidemiology, M.B. Bracken, ed. Oxford University Press, New York, 1984.

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Berkowitz, G.S., Kelsey, J.L., Holford, T.R. and Berkowitz, R.L. Physical activity and the risk of preterm spontaneous delivery. Journal of Reproductive Medicine, 28: 581-588, 1983.

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Holford, T.R., Brown, S.E. and Knudson, D.L. Estimation of DNA fragment size and generation of DNA restriction endonuclease maps using linear models. Journal of Virological Methods, 10: 117-126, 1985.

Roush, G.C., Schymura, M.J., Holford, T.R., White, C. and Flannery, J.T. Time period compared to birth cohort in Connecticut incidence rates for twenty-five malignant neoplasms. Journal of the National Cancer Institute, 74: 779-788, 1985.

Roush, G.C., Schymura, M.J. and Holford, T.R. Risk for cutaneous melanoma in recent Connecticut birth cohorts. American Journal of Public Health, 75: 679-682, 1985.

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Barnea, E.R., Holford, T.R. and McInnes, D.R.A. Log term prognosis of infertile couples with normal basic investigation -- Life table analysis. Obstetrics and Gynecology 66: 24-26, 1985.

Bracken, M.B., Bryce-Buchanan, C., Silten, R. and Holford, T. Menarcheal age and habitual miscarriage: Evidence for an association. Journal of the Society for the Study of Human Biology 12: 525-531, 1985.

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Coustan, D.R., Reece, E.A., Sherwin, R.S., Rudolf, M.C.J., Bates, S.E., Sockin, S.M., Holford, T.R., Taborlane, W.V. A randomized clinical trial of the insulin pump vs intensinve conventional therapy in diabetic pregnancies. Journal of the American Medical Association 255: 631-636, 1986.

INCIPAL INVESTIGATOR/PR)GRAM DIRECTOR:

BIOGRAPH.CAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE *(Mo., Day, Yr.)*
Brian Paul Leaderer	Assoc. Fellow, Assoc. Prof. Epidemiology (Env. Health)	

EDUCATION *(Begin with baccalaureate or other initial professional education and include postdoctoral training)*

INSTITUTION AND LOCATION	DEGREE *(circle highest degree)*	YEAR CONFERRED	FIELD OF STUDY
Manhattan College, New York City	B.S. (Eng.)	1968	Engineering
Yale University, New Haven, CT	M.P.H.	1971	Environmental Health
Yale University, New Haven, CT	Ph.D.	1975	Epidemiology & Environmental Health

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

1974	Consultant to National Academy of Sciences "Committee on Costs and Benefits of Automobile Emissions Control".
1975-76	Visiting Assistant Fellow - John B. Pierce Foundation Laboratory
1975-76	Research Fellow (Epidemiology & Environmental Health) - Dept. of Epidemiology and Public Health, Yale University School of Medicine.
1976-82	Assistant Fellow, John B. Pierce Foundation Laboratory
1976-82	Assistant Professor (Epidemiology & Environmental Health) - Dept. of Epidemiology and Public Health, Yale University School of Medicine.
1978-present	Member of Atmospheric, Microclimatology and Weather Committee of the Connecticut Academy of Science and Engineering.
1979	Consultant to National Academy of Sciences "Committee on Prevention of Significant Deterioration of Air Quality".
1979-present	Member and Vice Chairman of "Indoor Air Quality Committee" of the Air Pollution Control Association.
1982-present	Associate Fellow, John B. Pierce Foundation Laboratory Employer
1982-present	Associate Professor (Epidemiology & Environmental Health) - Dept. of Epidemiology and Public Health, Yale University School of Medicine.
1984	Chairman of Peer Review Committee of the U.S. Environmental Protection Agency (EPA) Research Program on Characterization of Indoor Air Contaminant and member and chairman of workshops to develop the U.S. EPA research program on indoor air quality.
1984-present	Reviewer of research grants for National Science Foundation and the U.S. Environmental Protection Agency.
1985-present	Advisor to New York State Energy Research and Development Authority on their Statewide Field Study of Infiltration and Indoor Air Quality.
1985-present	Consultant to Clean Air Scientific Advisory Committee (CASAC) of the Scientific Advisory Board of the U.S. Environmental Protection Agencies.
1985-present	Member National Academy of Science Committee on Passive Smoking.

Honors:

The Crosby Field Award (1984) for the best paper published by ASHRAE during 1983 and its contribution to the Society's technical literature.

Selected Full Length Publications Relevant to this Proposal:

Leaderer, B.P., et al. "Summary of the New York Summer Aerosol Study". J. Air Poll. Control Assoc., 28(3), pp. 321-328, 1978.

Leaderer, B.P., Holford, T.R. and J.A.J. Stolwijk. "Relationship Between Sulfate Aerosol and Visibility". J. Air Poll. Control Assoc., 29(2), pp. 154-159, 1979.

Zagraniski, R.T., Leaderer, B.P. and J.A.J. Stolwijk. "Ambient Sulfates, Photochemical Oxidants, and Acute Adverse Health Effects, An Epidemiological Study. Environmental Research, 19, pp. 306-320, 1979.

Leaderer, B.P. and J.A.J. Stolwijk. "Optical Properties of Urban Aerosol and Their Relation to Chemical Composition". In: Aerosols: Anthroprogenic and National - Sources and Transport. Ann. N.Y. Acad. Sci., Vol. 338, pp. 70-85, 1980.

Lioy, P.J., Samson, P.J., Tanner, R.L., Leaderer, B.P., Minnick, T. and W. Lyons. "The Distribution and Transport of Sulfate "Species" in the New York Metropolitan Area During the 1977 Summer Aerosol Study". Atmospheric Environment, Vol. 14, 1391-1407, 1980.

Leaderer, B.P. and J.A.J. Stolwijk. "Seasonal Visibility and Pollutant Sources in the Northeastern United States". Environ. Sci. Technol., Vol. 15, 305-309, 1981.

Leaderer, B.P., Tanner, R.L., Lioy, P.J. and J.A.J. Stolwijk. "Seasonal Variations in Light Scattering in the New York Region and Their Relation to Sources". Atmos. Environ., Vol. 15, 2407-2420, 1981.

Contributor to "Air Quality Criteria Document for Particulate Matter and Sulfur Oxides". U.S. Environmental Protection Agency, 1981.

Tanner, R.L., Leaderer, B.P. and J. Spengler. "Acid Aerosol in the Ambient Air". Environ. Sci. Technol. Vol. 15, 1150-1153, 1981.

Tanner, R.L. and B.P. Leaderer. "Seasonal Variability in Chemical Composition and Size Ditribution of Sulfate Aerosol in the New York Subregion". Atmos. Environ. Vol. 16, 569-580, 1982.

Leaderer, B.P., Tanner, R.L. and Holford, T.R. "Summer Diurnal Patterns of Aerosol Sulfate Composition at Four Locations in the N.Y.-N.J.-Conn. Tri-State Area and Their Relations to Ozone, SO_2 and Meteorological Variables". Atmos. Environ., Vol. 16, No. 9, 2075-2087, 1982.

Cain, W.S. and B.P. Leaderer. "Ventilation Requirements in Occupied Spaces During Smoking and Non-Smoking Occupancy". Environment International, Vol. 8 pp. 505-516, 1982.

Leaderer, B.P. "Air Pollution from Kerosene Space Heaters". Science, Vol. 218 pp. 1113-1115, 1982.

Leaderer, B.P. and Cain, W.S. "Air Quality in Buildings During Smoking and Non-Smoking Occupancy". ASHRAE Transactions Vol. 89, 28, pp. 601-613, 1983.

Cain, W.S., Leaderer, B.P., Isseroff, R., Berglund, L.G., Huey, R.J., Lipsitt, E. and D. Perlman. "Ventilation Reqirements in Buildings I. Control of Occupancy Odor and Tobacco Smoke Odor". Atmos. Environ., Vol. 17, No. 6, 1183-1197, 1983.

Leaderer, B.P., Cain, W.S., Isseroff, R. and Berglund, L.G. "Ventilation Requirements in Buildings. II. Particulate Matter and Carbon Monoxide from Cigarette Smoking". Atmos. Env., Vol. 17, No. 12, pp. 99-106, 1984.

Leaderer, B.P., Schapp, L. and Dietz, R.N. "Evaluation of the Perfluorocarbon Technique for Determining Infiltration Rates in Residents". Env. Sci. Technol., Vol. 19, No. 12, 1225-1232, 1985.

Leaderer, B.P., Zagraniski, R.T., Berwick, M. and Stolwijk, J.A.J. "Assessment of Exposure to Indoor Air Contaminants from Combustion Sources: Methodology and Application". American Journal of Epidemiology, Vol. 124, 1986. In press.

Leaderer, B.P. (Ed.) "Characterization of Air Contaminant Emissions from Indoor Sources". Atmospheric Environment, Vol. 20, No. 2, 1986. In press.

Leaderer, B.P. "Role of Source Characterization in Indoor Air Quality-An Overview". Atmospheric Environment, Vol. 20, No. 2, 1986. In press.

Hammond, S.K., Leaderer, B.P. and Roche, A. "Collection and Analysis of Nicotine as a Marker for Environmental Tobacco Smoke in Personal Samples". Atmospheric Environment, Vol. 20, No. 2, 1986. In press.

Leaderer, B.P., Hammond, S.K. and Tosun, T. Environmental tobacco smoke emission rates for RSP and nicotine. Proceedings 79th APCA, 86-80, 3, pp 1-12.

Cain, W.S., Tosun, T., See, L. and Leaderer, B.P. "Environmental Tobacco Smoke: Sensory Reactions of Occpants". Atmospheric Environment, Vol. 20, No. 2, 1986. In press.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR M ael Bracken

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Jean ellen McSharry	Project Coordinator	

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
University of Connecticut, Storrs	B.A.	1976	English Literature and Life Sciences

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

August 1980-March 1982 — Assistant in Research, Yale University School of Medicine, Perinatal Epidemiology Unit.
Collected data through patient interview and review of medical and laboratory records; interpreted results of lab tests and evaluated clinical significance of reported medical problems. Assisted with formulation of data collection instruments; development of coding systems; development of protocols for selection of study subjects and for collection of data through hospitals and clinics.

August 1980-May 1984 — Assistant in Research, Perinatal Epidemiology Unit.
Responsibilities same as above.

June 1984-present — Assistant in Research, Perinatal Epidemiology Unit, Project Coordinator, Male Subfertility study.
Administer and supervise the daily activities of an eight person research team. Organize hiring and training of new staff members. Establish work priorities for and supervise research assistants and office staff. Review all data for completeness and coding consistency. Document all coding decisions. Work with data manager to determine status of data entry and to resolve any data entry problems. Report weekly to P.I. on overall progress of data collection.

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OTHER SUPPORT

(Use continuation pages if necessary)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications and proposals pending review or funding; (3) applications and proposals planned or being prepared for submission. Include *all* Federal, non-Federal, and institutional grant and contract support. If none, state "none." For each item give the source of support, identifying number, project title, name of principal investigator/program director, time or percent of effort on the project by professional named, annual direct costs, and entire period of support. (If part of a larger project, provide the titles of both the parent project and the subproject and give the annual direct costs for each.) Describe the contents of each item listed. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, delineate and justify the nature and extent of the scientific and budgetary overlaps or boundaries.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: Michael B. Bracken

(1) ACTIVE SUPPORT:

NS15978-07 National Acute Spinal Cord Injury Study, P.I., M.B.Bracken, 25%, 8/1/84 to 7/31/88 - $396,427.

HD 16282-03 Environmental Risk Factors Related to Male Subfertility, P.I., M.B.Bracken, 25%, $169,659, 7/1/83 to 6/30/87.

(2) PENDING:

(1) ACTIVE SUPPORT: Theodore R. Holford

51103
CA00875-03 Preventive Oncology Academic Award, P.I., George Roush, 30%, 8/1/83 - 7/31/88 - $70,424.

51638
CA30931-05A1 Systematic Analysis Connecticut Cancer Incidence Trends, P.I. Theodore Holford, 20%, 8/1/81 - 11/30/88 - $95,129.

51192
5RO1 HD 16282-03 Environmental Risk Factors Related to Male Subfertility, P.I., M.B.Bracken, 10%, 7/1/83 - 6/30/87, $169,659.

51932
1RO1 CA39477-01 An Epidemiologic Study of Multiple Primary Breast Cancer, P.I., W. Douglas Thompson, 10%, 4/1/85 - 3/31/88 - $176,161.

51152
5T32CA09279-08 Cancer Epidemiology and Biostatistics, P.I., Theodore Holford, 20%, 9/1/83 - 8/31/88 -

(1) ACTIVE SUPPORT: Kathleen Belanger
HD 16282-03 National Acute Spinal Cord Injury Study, P.I., M.B.Bracken 100%, 8/1/84 - 7/31/88 - $396,427
(1 year post doctoral research position)

(2) PENDING

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OTHER SUPPORT

(Use continuation pages if necessary)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications and proposals pending review or funding; (3) applications and proposals planned or being prepared for submission. Include *all* Federal, non-Federal, and institutional grant and contract support. If none, state "none." For each item give the source of support, identifying number, project title, name of principal investigator/program director, time or percent of effort on the project by professional named, annual direct costs, and entire period of support. (If part of a larger project, provide the titles of both the parent project and the subproject and give the annual direct costs for each.) Describe the contents of each item listed. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, delineate and justify the nature and extent of the scientific and budgetary overlaps or boundaries.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:

(1) ACTIVE SUPPORT: (Dr. Brian Leaderer)

NIH Grant ES 00354: "Human Responses to the Indoor Environment"; P.I. J.A.J. Stolwijk; Percent of Effort, Dr. Leaderer 80%; Annual Direct Costs $506,586 (7/1/84 - 6/30/86); Project Direct Costs $1,696,900 (7/1/82 - 6/30/86).

EPA Gas Research Institute: "Characterization of Indoor Sources of Air Contaminants"; P.I. Dr. Brian Leaderer; Percent of Effort 5%; Annual Direct Costs $52,650 (4/8/85 - 9/30/86); EPA Contract #CR-812389-01-0.

PROPOSALS PENDING:

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RESOURCES AND ENVIRONMENT

FACILITIES: Mark the facilities to be used at the applicant organization and briefly indicate their capacities, pertinent capabilities, relative proximity and extent of availability to the project. Use "other" to describe the facilities at any other performance sites listed in Item 9, page 1, and at sites for field studies. Using continuation pages if necessary, include an explanation of any consortium arrangements with other organizations.

☐ Laboratory:

☐ Clinical:

Office space is available for this study in the Yale Perinatal Epidemiology Unit. Dr. Bracken is Director of the Unit and Professor in the Departments of Epidemiology and Public Health and Obstetrics and Gynecology. The unit is connected by direct line to the Yale Computer Center.

☐ Animal:

The Yale Computer Center is available to the entire university community on a fee for service basis according to a uniform rate schedule. The facility operates an IBM system 370/model 158 and IBM 4341 with on-site and remote capability for batch and interactive service.

☒ Computer:

The biochemical and aerometric samples will be analyzed at the John B. Pierce Foundation under the direction of Dr. Leaderer. The Pierce Foundation is an affiliate of Yale University and located adjacent to the Yale Medical School. Staff of the Foundation may hold faculty appointments in the Department of Epidemiology and Public Health where Dr. Leaderer is an Associate Professor. Yale University and the Foundation operate their financial affairs independently - hence the need to subcontract Dr. Leaderer's expenses in this application.

☒ Office:

☐ Other (_____):

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

ADDITIONAL INFORMATION: Provide any other information describing the environment for the project. Identify support services such as consultants, secretarial, machine shop, and electronics shop, and the extent to which they will be available to the project.

2023488447

A. Specific Aims

1. To test the hypothesis that pregnant women passively exposed to someone else's tobacco smoke are at increased risk of delivering an infant with low birthweight, or before 37 weeks gestation, and/or with intrauterine growth retardation (IUGR). The relationship between passive smoke exposures and perinatal outcomes will be evaluated in detail for evidence of a dose relation, for any interactive effects between direct and passive smoke exposure, and for differential effects due to exposure at different stages of pregnancy. Evidence of for any effect of passive smoking on perinatal outcomes will have important implications for public health policy.

2. To examine this hypothesis while adjusting for other factors known to increase the risk of IUGR including: direct smoking, the use of alcohol, marijuana, cocaine or other drugs; maternal diseases such as diabetes, hypertension, pancreatitis and renal disease; maternal factors such as race, previous pregnancy history, height, weight, and weight gain during pregnancy. The main effects, of the more prevalent of these factors, on the study outcomes will also be determined, as well as any interactions between these risk factors and direct or passive smoke exposure. Additionally, the effects of direct maternal smoking on perinatal outcomes will be estimated, with more precision than is usually possible, by contrasting the offspring of direct smokers with those of women exposed neither directly nor passively.

3. To evaluate the validity of different measures of environmental smoke exposure. Exposure will be measured by questionnaire, by personal nicotine monitors and by urinary cotinine, a biochemical marker of exposure. The home environment of a subset of women will also be assessed. Each of these methods will be compared with the others. A purposeful sample (n=300) of subjects will be used to study evidence of direct fetal passive smoke exposures through measurement of cotinine in amniotic fluid and cord blood. This study will be the first to correlate questionnaire data, aerometric measures and biochemical markers, and will provide important methodological data for future studies of environmental tobacco smoke.

4. We will also collect detailed information about marijuana use through out pregnancy in order to test a hypothesis that maternal use of marijuana is related to increased risk of IUGR in offspring. Portions of each maternal urine sample will be saved for later testing of Δ 9-THC metabolites as evidence of marijuana smoking with gas chromatography/mass spectrometry confirmation in subsamples (funding for which is not requested in the present application).

B. Significance

Smoking during pregnancy has been associated with a number of adverse reproductive outcomes, including low birthweight (1,2), spontaneous abortion (3), placenta previa and abruptio (4), and neonatal death (1,5). Of these, low birthweight has been most consistently associated with maternal smoking. Women who smoke, on average, give birth to infants 150-200 grams lighter than women who do not smoke (2). This difference appears to be primarily due to an increase in intrauterine growth retardation (IUGR) rather than preterm delivery, although the latter has been implicated in some studies (1).

The proportion of women who smoke during pregnancy is approximately 30 percent (1). Of additional concern, however, are recent studies indicating that non-smokers, exposed to someone else's smoke (passive smoking), may be at increased risk of the same health hazards as smokers. Two studies (6,7) have indicated an increased risk of lung cancer among non-smoking wives of smokers, although this was not confirmed in a third study (8). Children have been found to have increased rates of pneumonia and bronchitis in the first year of life (9,10), as well as asthma (11) and other respiratory illnesses (12), when their parents smoke. Passsive smoke exposure during childhood may also effect growth. Rona et al. (13) have shown that the height of children is associated with the number of smokers in the household, independent of birthweight, maternal smoking during pregnancy and social class.

Although levels of various smoke contaminants, including carbon monoxide and nicotine, have been shown to be higher in sidestream than in mainstream smoke (14), measuring exposure to passive smoking is complicated, depending not only of the duration and intensity of the exposure but also on the ventilation characteristics of the building (15). Early studies used the smoking history of the spouse, or the number of smokers in a household, as a proxy measure of passive smoke exposure. However this approach ignores exposures from other sources, such as friends or co-workers, and usually does not consider the amount that the spouse smokes while in the company of the non-smoker. Friedman et al. (16) report that 40-50 percent of persons with non-smoking spouses report some passive smoke exposure, while 30-35 percent of persons married to smokers report no exposure. Thus, these traditional measures of passive smoke exposure incur considerable misclassification.

Biochemical markers have also been used as a measure of passive smoke exposure, including carboxyhemoglobin, nicotine, cotinine and thiocyanate. Carboxyhemoglobin is not considered a reliable measure since it is affected by sources of carbon monoxide other than tobacco smoke (17). Thiocyanate, may be a good indicator of chronic exposure since it has a relatively long half-life (14 days) (18), however assays are not sensitive at low levels and are thus inappropriate to measure environmetal smoke exposures. Nicotine and cotinine (a metabolite of nicotine) are the most specific indicators of exposure to tobacco smoke (18), and of these cotinine has a longer half life (2 days vs 30 mins) and can be measured at low levels in serum, saliva, and urine. Cotinine urine levels are also highly correlated with cotinine blood levels (19). There are no studies in the literature which validate exposure data from questionnaires with biochemical and air monitoring data.

Recent studies have attempted to determine whether the fetus is exposed to measurable amounts of tobacco smoke when the mother is passively exposed. Three investigators (20,21,22) have detected cotinine in amniotic fluid withdrawn for amniocentesis, of women passively exposed to tobacco. Bottoms et al. (23) obtained fetal blood from the umbilical cord at the time of delivery and compared thiocyanate levels among women who smoked, who had a smoker in the household, and women with "no exposure." The distribution of fetal thiocyanate levels was significantly higher in the passive smoking group than in the no exposure group, similarly fetal thiocyanate levels were significantly higher in the active smoking group than in the passive exposure group. A similar study was conducted by Hauth et al. (24). These authors did not find a significant difference in fetal thiocyanate levels comparing the passive exposure and no exposure groups

Although the association of low birthweight with maternal smoking is well established, few studies have examined the effect of passive smoking on birthweight and growth retardation. As mentioned above, early studies approached this problem by considering paternal cigarette smoking and birth outcomes. Yerushalmy (25) reported that when the father smoked there was an increase in the proportion of infants born weighing less than 2500 grams, and this proportion increased directly in relation to the amount the father smoked. When maternal smoking was considered, the increase risk of a low birthweight infant was confined to families with both parents smoking.

McMahon et al. (26) showed that infants of fathers who smoked had a mean birthweight 3 ounces (85 grams) less than those whose fathers were non-smokers. However when the data was standardized to the distribution of non-smokers,the difference was reduced to 0.4 ounces (11 grams) and 1.0 ounces (28 grams) for males and females, respectively. The authors concluded that all or nearly all of the difference was explained by the correlation between smoking habits of the parents.

Underwood et al. (27), who examined the smoking habits of both parents in a study of 48,505 pregnancies among wives of naval personnel, reported that smoking by the father did not influence the risk of low birthweight. Similarly, Terris and Gold (28) found no effect of paternal smoking in a study of prematurity.

These studies used an inadequate proxy measure of fetal exposure and did not control for several very significant risk factors for low birthweight including social class, race (except 28), and the previous birth of a low birthweight infant. Thus, the risk to the fetus of environmental tobacco smoke continues to be poorly understood.

Data from the Yale study (to be described below) suggests that one quarter of all pregnant women, who are not smokers themselves, may be exposed to other persons tobacco smoke. Should passive smoke exposure be confirmed as a perinatal risk factor its high prevalence would give it considerable importance in explaining the population incidence of IUGR. Additionally, clarification of the independent effects of passive smoke exposure would inable us to improve estimation of the effect of direct smoking. Almost without exception, studies of direct smoking consider women to be "unexposed" even though they may be passively exposed. Thus,

passive smoke effects may spuriously reduce relative risks due to direct smoking. In the Yale study, the risk of direct smoking on IUGR rose from 1.86 using all non-smokers as unexposed to 3.54 when only women exposed neither directly nor passively were considered unexposed.

C. Preliminary Studies

We have examined the hypothesis that pregnant women passively exposed to tobacco smoke have an increased risk of infants with low birthweight and intrauterine growth retardation (IUGR) using data from the Yale Pregnancy Outcome Study (29). This was a large prospective study designed to investigate the relationship of pregnancy outcome to a variety of exposures. Between May 12, 1980 and March 12, 1982, 4186 pregnant women, who intended to deliver at Yale New-Haven Hospital were interviewed. The interview information included pregnancy history, demographic characteristics, contraceptive practice, medical history, and exposure to other possible risk factors. Most interviews were conducted in the women's homes and took place within a few weeks of the women's first prenatal visit.

Data regarding pregnancy outcome and the condition of the newborn were abstracted from the mothers' and infants' medical charts for 3,891 live, singleton deliveries. Information on birth weight and gestational age was not available on 33 and 10 infants respectively, limiting the analysis for each outcome to 3,858 or 3,881 singleton births. We examined the association of passive smoking with low birth weight (<2500 g) and preterm delivery (<37 weeks gestational age from last menstrual period), as well as the effect on mean birth weight and mean gestational age. Intrauterine growth retardation was examined using the rate of low birth weight in term deliveries (>36 weeks gestational age). Passive smoking was defined as being exposed to someone else's cigarette smoke for at least two hours per day, either at home or at work, during pregnancy.

Table 1 shows the distribution of maternal characteristics by four groups of smoke exposure: none, passive only, direct only, or both passive and direct. About one-fourth of the women had not smoked cigarettes during pregnancy but had been exposed to sidestream smoke for at least two hours per day. Chi-square analysis resulted in significant differences between the four exposure groups on age, marital status, ethnicity, education, employment, use of alcohol, caffeine, and marijuana, parity, history of induced abortion, weight gain, and body mass index.

Among all nonsmokers, passive smokers were compared to other nonsmokers on the maternal characteristics by chi-square analysis. Those who were passive smokers were significantly more likely to be: young, single, nonwhite, not college educated, employed, and nulliparous (all $p<0.0001$). They tended to have consumed more caffeine ($p<0.003$), smoked marijuana ($p<0.04$), not used alcohol ($p<0.002$), had a history of induced abortion ($p<0.008$), gained less than 10 kg or more than 20 kg ($p<0.0006$), and been of higher weight to height ratio ($p<0.0002$). They did not differ significantly on histories of spontaneous abortion or stillbirth.

The crude associations between passive smoking and mean birth weight and the rate of low birth weight, showed a significant effect on mean birth weight among nonsmokers ($\Delta=61$ g, $z=2.84$, $p=0.005$) but not among

smokers (Δ=34 g, z=1.08, p=0.28). Among nonsmokers the rate of low birth weight increased from 3.00 per cent to 3.91 per cent with exposure to passive smoke (Relative Risk [RR]=1.30, 95% Confidence Interval [CI]=0.85, 1.98). Among smokers the respective low birth weight rates were 6.06 and 6.10 per cent. The crude associations between passive smoking and mean gestational age and the rate of preterm delivery showed no significant differences between the exposed and unexposed groups (preterm delivery rates of 4.64 and 4.66 per cent in, respectively, nonsmokers not passively and passively exposed; respective rates in smokers being 6.67 and 6.58 per cent).

When the effect of passive smoking on mean birth weight and low birth weight are each examined, stratified by term or preterm deliveries, the only significant associations are in nonsmokers having term infants, suggesting an effect on growth retardation (table 2). The rate of low birth weight in term infants increased monotonically from 0.86 per cent in those not exposed to passive or direct smoke to 3.27 per cent in those exposed to both.

The associations in nonsmokers having term infants were analyzed using multiple linear regression and multiple logistic regression to control for the effects of confounding variables. All of the variables in table 1 were analyzed. The final model reached by logistic regression included the passive smoking variable and four confounders: the continuous variables for gestational age and maternal age, as well as dichotomous variables for parity (0 vs >1), and race (nonwhite vs white) (table 3). The adjusted relative risk of having a low birth weight baby for passive smokers was 2.17 (95 per cent CI=1.05, 4.50).

The final model achieved by linear regression included the passive smoking variable and three confounders: the continuous variables for gestational age and dichotomous variables for parity and race. Passive smoking was associated with a decrease in mean birth weight of only 24 grams which was not statistically significant, having a p-value of 0.20 (table 4).

Maternal weight gain and body mass index were not used in these regression models because there were missing values on about one-fourth of the subjects. When the analysis was performed on the subset of women with weight information the passive smoking estimates were only slightly diminished with weight gain in the model. This suggested that weight gain was not confounding the effect so we eliminated this variable from the models to avoid unnecessary loss of statistical power.

Regression models were repeated on all subjects having term infants, controlling simultaneously for both direct and passive smoking. There was no significant interaction between these two variables. The overall adjusted relative risk for passive smoking was 1.52 (95 per cent CI=0.90, 2.56; p=0.12), while that for direct smoking was 1.86 (1.10, 3.15 g; p=0.02). The adjusted mean decrease in birth weight for passive smoking compared to no exposure was 30 g (0.1, 60 g; p=0.05), while that for cigarette smokers compared to nonsmokers was 137 g (105, 170 g; p=0.0001).

Although passive smoking showed no effect on mean gestational age or preterm delivery in the crude associations, regression analyses were performed to determine whether such an association was obscured by

TABLE 1
Distribution of maternal characteristics by smoke exposure during pregnancy, Yale-New Haven Hospital, 1980–1982

Characteristic	n*	Smoke exposure				Significance test
		None	Passive	Direct	Both	
(No. of subjects)	(3,641)	(1,707)	(908)	(436)	(792)	
Total subjects (%)	100.0	44.4	23.6	11.4	20.6	
Age (years)						
<20	388	5.3	11.7	16.9	16.6	
20–24	861	13.9	24.1	28.3	34.3	$\chi^2 = 315.2$, df = 12; $p = 0.0001$
25–29	1,425	40.2	36.1	33.6	31.2	
30–34	972	33.1	21.6	18.1	16.1	
≥35	204	7.4	4.5	3.2	2.8	
Marital status						
Currently married	2,966	88.3	78.6	63.9	66.5	$\chi^2 = 238.6$, df = 6; $p = 0.0001$
Divorced, separated, or widowed	140	2.5	3.2	4.1	6.3	
Single	712	9.2	21.3	32.0	28.2	
Ethnicity						
White	2,960	86.0	71.5	68.1	74.5	$\chi^2 = 106.6$, df = 6; $p = 0.0001$
Black	713	12.0	25.4	27.6	22.3	
Other	140	2.9	6.1	4.4	3.2	
Education (years)						
<12	631	8.3	12.8	24.6	25.4	$\chi^2 = 547.4$, df = 9; $p = 0.0001$
12	1,074	18.7	33.4	34.9	37.8	
13–16	1,631	48.9	42.6	32.9	33.8	
≥17	906	28.1	11.4	7.8	3.0	
Current employment						
Employed	1,937	51.6	60.6	34.7	46.1	$\chi^2 = 86.8$, df = 3; $p = 0.0001$
Not employed	1,484	48.4	39.4	65.3	53.9	
Cigarettes (daily)						
1–10	637			57.2	60.4	$\chi^2 = 5.0$, df = 2; $p = 0.0821$
11–20	435			32.7	27.9	
21+	134			10.1	11.7	
Alcohol (oz/day)						
None	1,194	31.5	38.8	27.8	22.5	$\chi^2 = 88.6$, df = 6; $p = 0.0001$
≤0.25	2,333	61.2	54.1	62.1	65.6	
>0.25	313	7.0	6.1	10.1	11.5	
Caffeine (mg/day)						
None	896	27.5	23.9	18.8	15.6	$\chi^2 = 249.5$, df = 9; $p = 0.0001$
1–150	1,866	53.2	50.9	44.1	40.9	
151–300	730	15.5	18.2	22.8	24.2	
≥301	350	3.8	6.0	13.3	19.2	
Marijuana						
None	3,464	95.1	92.7	86.9	79.7	$\chi^2 = 171.8$, df = 6; $p = 0.0001$
1–3 times/month	239	3.7	5.2	7.6	12.1	
1+ times/week	133	1.2	2.1	6.5	8.2	
Parity						
0	1,765	41.6	53.2	42.1	48.2	$\chi^2 = 56.9$, df = 9; $p = 0.0001$
1	1,297	37.2	31.4	32.2	28.9	
2	457	11.9	8.3	16.8	10.7	
3+	342	9.3	7.1	9.0	10.2	
Previous spontaneous abortion(s)	656	17.3	15.9	18.6	17.4	$\chi^2 = 1.7$, df = 3; $p = 0.6482$
No history	3,163	82.7	84.1	81.4	82.6	
Previous induced abortion(s)	822	17.2	21.5	28.0	26.8	$\chi^2 = 43.6$, df = 3; $p = 0.0001$
No history	2,019	82.8	78.5	72.0	73.2	
Previous stillbirth(s)	34	0.8	0.6	1.2	1.0	$\chi^2 = 1.7$, df = 3; $p = 0.6437$
No history	3,807	99.1	99.4	98.8	99.0	
Weight gain (kg)						
0–10	668	14.0	18.0	21.1	23.6	$\chi^2 = 61.4$, df = 9; $p = 0.0001$
11–15	1,313	47.3	40.1	40.6	32.9	
16–20	903	28.4	28.8	24.8	29.8	
≥21	358	9.3	12.1	13.5	13.9	
Body mass index (kg/m²)						
<19	370	14.4	12.3	13.3	14.8	$\chi^2 = 21.2$, df = 6; $p = 0.0017$
19–26	1,778	68.4	63.6	66.0	62.7	
>26	536	16.2	24.1	20.6	22.5	

*Smoke exposure data were missing on 60 subjects.

TABLE 2

Mean birth weights and rates of low birth weight for passive smoke exposure by cigarette smoking status for term deliveries, Yale-New Haven Hospital, 1980–1982

Cigarette smoking	Passive smoking	n	Mean birth weight† (g)	$\bar{X}_e - \bar{X}_u$ (95% CI)‡	Low birth weight§ (%)	Crude relative risk	95% CI§
No	No¶	1,620	3,507	75 g	0.86	1.00	
	Yes	863	3,422**	(33.3–113.0)	2.34	2.72*	1.38–5.36
Yes	No¶	401	3,336	41 g	2.99	1.00	
	Yes	736	3,256	(−14.0–96.0)	3.27	1.09	0.55–2.16

* $p < 0.005$.
** $p < 0.0002$.
† Compared by two-tailed z score.
‡ 95% confidence interval (CI) = $(\bar{X}_e - \bar{X}_u) \pm 1.96\ (SD\sqrt{1/N_e + 1/N_u})$.
§ Compared by chi-square analysis.
‖ 95% CI = relative risk $\exp \pm 1.96\ ((1 - Re)/(Re)(Ne) + (1 - Ru)/(Ru)(Nu))$, where Re = rate in exposed, Ne = no. in exposed, Ru = rate in unexposed, and Nu = no. in unexposed.
¶ Reference category.

TABLE 3

Effects of passive smoke exposure and other risk factors on low birth weight according to logistic regression, in nonsmokers having term deliveries, Yale-New Haven Hospital, 1980–1982

Parameter	Estimate (β)	Adjusted relative risk	95% CI**	p value
Passive smoke exposure	0.7749	2.17	1.05–4.50	0.0370
Gestational age*†	−0.6028	20.35	5.70–70.70	0.0000
Parity 0‡	0.7519	2.13	0.99–4.53	0.0521
Maternal age*§	0.0777	3.21	1.05–9.87	0.0391
Nonwhite ethnicity‖	1.5831	4.87	2.21–10.74	0.0001

* Continuous variable.
** 95% confidence interval (CI) (categorical) = $\exp[\beta \pm 1.96$ (standard error (SE))]. 95% CI (continuous) = $\exp[\beta(X1) \pm 1.96(SE)X1)/\exp(\beta(X0) \pm 1.96(SE)X0)]$ where X1 = value of variable to be compared to reference and X0 = reference value.
† 35 weeks compared with 40 weeks gestation used to calculate relative risk.
‡ Compared with parity 1+ to calculate relative risk.
§ 35 years of age compared with 20 years to calculate relative risk.
‖ Black and other compared with white ethnicity.

TABLE 4

Effects of passive smoke exposure and other risk factors on mean birth weight according to linear regression, in nonsmokers having term deliveries, Yale-New Haven Hospital, 1980–1982

Parameter	Adjusted mean difference in birth weight (β)	95% CI†	p value
Passive smoke exposure	−23.5	−69.9–12.8	0.2050
Gestational age*‡	86.9	76.4–97.4	0.0001
Parity 0§	−148.5	−183.0–−113.9	0.0001
Nonwhite ethnicity‖	−249.0	−293.0–−205.0	0.0001

* Continuous variable.
† 95% confidence interval (CI) = $\beta \pm 1.96$ (standard error (SE) of β).
‡ Increase in grams per week of gestation.
§ Compared with parity of 1 or more for calculation of relative risk.
‖ Black ethnic groups and other compared with white.

confounding factors. However, no effects of passive smoking on these pregnancy outcomes were found.

This study has several advantages over the previous investigations of low birth weight and passive smoking. They examined pregnancy outcomes in relation to the husband's smoking status, rather than to the woman's actual exposure to sidestream smoke, which may have occurred independently of the husband's smoking. Some husbands may have smoked but not in the presence of their pregnant wives, while other women with nonsmoking husbands may have been exposed to passive smoke of other people.

The women interviewed in our study responded to whether or not they were exposed for at least two hours per day during pregnancy to someone else's smoke, either at home or at work. This classification attempted to define a group who was truly exposed, even though duration beyond two hours and intensity of exposure for each woman is unknown. Some misclassification is a potential problem because of the difficulty in precisely estimating hours per day of exposure. Ideally, it would have been desirable to have some measure of dose, either by more detailed questioning of the women or by assaying a biochemical marker for exposure.

Our results suggest that passive smoking during pregnancy doubles a nonsmoker's risk of having a growth retarded infant. This association was not explained by the effects of age, parity, or race. This risk is approximately the same as that usually found for maternal cigarette smoking when compared with all nonsmokers (1). It is of interest to note that the risk of direct smoking alone (ie. not passively exposed), when compared with women exposed neither directly nor passively, increases to 3.54 (95 per cent CI=1.62, 7.71). Analysis of all subjects resulted in a risk for passive exposure, controlling for cigarette smoking, of 1.52 which is slightly less than that observed in only nonsmoking mothers but is still elevated. This reduction in risk in the pooled data is not surprising since there was no additive effect of passive smoking among direct smokers. The adjusted risk of having a growth retarded infant for cigarette smokers in our sample, when compared with all nonsmokers, was 1.86, which is similar to that observed in other studies.

Passive smoking had little effect on mean birth weight among nonsmokers having term births, decreasing it by only 23.5 g, with other factors taken into account. In all term births, the adjusted decrease in mean weight due to passive smoking (30g) was approximately one-fourth of that due to direct smoking during pregnancy (137 g). While this may not overall be a clinically meaningful decrease in weight, it appears to operate at the low end of the birth weight distribution, thereby increasing the risk that the infant will weigh less than 2,500 g, and, therefore, be more likely to die during the perinatal period (26).

Survey of Findings - Exposure Assessment

In epidemiologic studies of air contaminants, it is important to specify the exposure to specific particulates or gasses on the time scale corresponding to the health effect sought. The impact of exposure to an air contaminant should, ideally, be evaluated in terms of the dose of the contaminant or its metabolites received by the target tissue. This,

however, in virtually all cases is not practical logistically or because of limitations in our knowledge in the uptake, distribution, metabolism, site and mode of action of the contaminant(s) in humans. In the absence of an ability to measure or specify the dose of a contaminant received, exposures are assessed by using biological markers measured in the subject population, by personal monitors or by an monitoring of the micro-environments (residences, workplace, etc) in which people spend their time.

Our research efforts over the past three years have been directed toward:

a) developing a general methodology for assessing indoor air pollutant exposures in support of epidemiologic studies.
b) characterizing environmental tobacco smoke (ETS) chemically and identifying proxy or tracer contaminants indicative of ETS exposure.
c) developing air monitoring methods which would permit the easy and inexpensive monitoring of both personal exposures and indoor space concentrations of environmental tobacco smoke.

a) Exposure Assessment Methodology

A general methodology has been developed for assessing indoor air pollutant exposures to unvented combustion by-products (30). This methodology was applied on a pilot basis to assessing exposures to air contaminants generated by unvented kerosene space heaters in 333 residences in the New Haven, Connecticut area during the 1982-1983 heating season. The field study protocol serves as a prototype of a nested design of exposure assessment or estimation which could be applied to a large-scale field study of indoor air contaminant levels from combustion sources, particularly for ETS.

The exposure assessment was conducted in two phases. The first phase included structured personal interviews of all participants. Data gathered included the number, type and usage of indoor sources of air contaminants (e.g., kerosene heaters, gas stoves, toabcco smoking); and the physical (insulation, storm windows, etc.) and heating characteristics (type of central heat, temperature settings, number of thermostats, etc.) of residences. Data from this phase was used to characterize individuals into exposure categories.

The second phase was a nested design, conducted over a 12 week period (six two-week periods) in which exposures were assessed. Four levels of monitoring were used (figure 1) with increasing precision to assess air contaminant exposures and the primary factors influencing them. The first level consisted of biweekly telephone reports from all participants on source use and acute respiratory disease (the health outcome variable under study). The second level of monitoring consisted of passively measuring NO_2 levels (the primary air contaminant associated with the indidence of respiratory disease) in residences for at least one two-week period. Each matched pair of residences, exposed (with a kerosene heater) and unexposed or control (without a kerosene heater), was treated as a unit, randomly assigned to one of the six two-week periods and monitored in that period for NO_2. The third level of monitoring collected more detailed exposure data in a subset of approximately 10 homes in each two week period and consisted of

1) two-week average levels of SO_2, formaldehyde and NO_2; 2) a daily diary on source use; 3) a kerosene sample for sulfur content determinations; 4) two-week average infiltration rates, and, 5) personal total NO_2 exposures via a passive NO_2 monitor worn by an adult in the household. The fourth level of monitoring consisted of continuously monitoring 14 selected homes (volunteers) during periods II-VI for nitric oxide, NO_2, CO, SO_2, CO_2, per cent oxygen depletion, temperature and humidity over a period of time ranging from a few days to a week. These homes received the full complement of monitoring received in the other levels.

A detailed presentation of the nested exposure assessment protocol employed in the above field study along with the measured concentrations and an evaluation of the protocol can be found in a recent publication (30). One important outcome of the protocol employed is that it permits the estimation of exposures in residences during periods when air sampling is not conducted, based upon the telephone questionnaire of source use (stage I) and the period during which air sampling was conducted in the residence.

The design of the biochemical and aerometric exposure assessment for the proposed epidemiologic study on passive smoking (see Methods Section) is based upon the exposure assessment methodology developed for the kerosene heater field study outlined above. The one major difference is that the proposed ETS study will utilize cotinine measurements as a biological marker of ETS exposure to compliment the personal monitoring, indoor space monitoring, and source use questionnaires.

b) Characterization of ETS

Environmental tobacco smoke is a major source of both respirable suspended particulate matter (RSP) and volatile organic compounds (VOCs) in both the residential and non-industrial occupational indoor environment. The broad range of air contaminants in ETS (over 3,000 compounds found in both particulate and vapor phase) and the existence of other possible indoor sources for many of those contaminants makes it difficult to assess the contribution of ETS to air contaminant levels measured indoors or by personal monitoring.

Assessing the contribution of ETS to air contaminant levels measured requires the identification of a proxy or tracer air contaminant indicative of ETS. The proxy contaminant must be unique to tobacco smoke, a major constituent of the smoke, efficiently and easily collected in air sampling, efficiently extracted from the collected samples and easily analyzed with high sensitivity. Use of that proxy to represent exposure to individual or groups of air contaminants from tobacco combustion requires that the proxy contaminant be found in a fairly consistent ratio to the ETS class of contaminants of interest for a number of different brands of cigarettes under a variety of environmental conditions.

In a series of experiments conducted in our 34 m^3 environmental chamber we have investigated the use of nicotine as a potential proxy or marker to represent ETS related contaminants in general and, more specifically, the respirable suspended particulates in ETS. Nicotine is present in all cigarette smoke and is a major constituent, after water, in

the smoke. Virtually the only source of nicotine in nearly all environments is cigarette smoke. Sensitive means exists for analyzing nicotine such that is can be detected a very low concentrations in small volumes of sampled air. In addition, the occurrence of nicotine and that of its major metabolite, cotinine, in biological fluids is entirely due to active or passive smoking. Thus, the use of nicotine as a proxy for ETS exposure would permit exposure assessment via both concentrations in the physical environment and biological marker measurements.

In one set of experiments (31) in our chamber we evaluated the partitioning of nicotine in environmental tobacco samples for 6 different brands of cigarettes with varying FTC mainstream nicotine ratings and at concentrations typical of "real world" conditions. Under steady-state conditions with constant smoking rates by occupants and constant temperature and humidity particulate and vapor phase nicotine concentrations were determined over a four hour sampling period. A new active nicotine sampling technique, described in the next section of this progress report, was used in this study. Table 5 shows the total nicotine measured, the particulate phase, nicotine, the gas phase nicotine and the per cent nicotine in the gas phase for each experiment.

The results of these experiments indicates that nicotine in ETS is predominately in the vapor phase. A recent independent study using a different experimental design and air sampling methodology arrived at the same conclusion (32). This finding forms the basis of our newly developed passive monitor for nicotine which would permit the monitoring of personal nicotine exposures and nicotine concentrations in indoor spaces.

In a separate set of environmental chamber experiments using a protocol similar to that described above for the nicotine partitioning experiments ETS emission rates for RSP and nicotine were measured for 12 brands of cigarettes (for a range of FTC tar and nicotine ratings), and one cigar (31). This set of experiments was also conducted to evaluate the feasibility of using nicotine as a proxy for the RSP in ETS. Table 6 shows the results of those experiments. There are a number of major findings from this study:

1) ETS emission rates for RSP and nicotine for the brands of cigarettes tested show little variability and do not relate to the highly variable mainstream emission FTC ratings.
2) little variability in the emission rates of RSP and nicotine were observed for different runs of the same cigarette done on separate days (one cigarette has three runs while another cigarette, U of Ky 1R3F, has two runs).
3) the ratio of nicotine to RSP for the brands of cigarette, while exhibiting variability, are within a fairly narrow range suggesting that nicotine may be a good indicator of exposure to respirable suspended particulate mass from ETS.
4) the cigar has substantially higher emission rates for RSP but nicotine emission rates within the range of those observed for cigarettes.

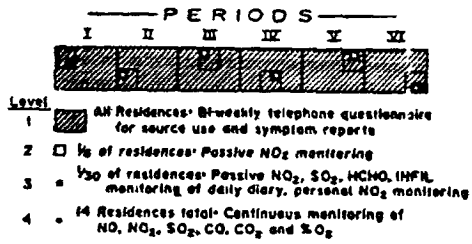

Figure 2. Nested protocol in four levels to assess indoor combustion by-product exposures related to unvented sources in 302 homes, New Haven, CT., area winter 1983. Abbreviations: HCHO, formaldehyde; INFL, infiltration rate determinations; NO, nitrogen oxide; CO, carbon monoxide; CO_2 carbon dioxide; $\%O_2$, percent oxygen depletion.

Table 5
Partitioning of Nicotine in Environmental Tobacco Smoke

Sample #	Particulate Nicotine (g)	Vapor Nicotine (g)	Total Nicotine (g)	Vapor/Total Nicotine (%)
A	1.3	43.1	44.4	97
B	1.2	42.3	43.6	97
C	0.9	40.3	41.2	98
D	0.3	45.1	45.4	99
E	1.0	28.4	29.4	97
F	1.2	30.2	31.4	96

Table 6
Emission Factors for RSP and Nicotine From Tobacco Combustion (ETS)

Tobacco* Type	Tar	Nicotine	RSP Emissions mg/g smoked	Nicotine Emissions mg/g smoked	Ratio of Emissions ug Nicotine/mg RSP
cig**	23	1.3	30± 1.9	1.9± 0.1	63
cig***	-	-	35± 3.7	2.7± 0.3	77
cig	17	1.3	28± 3.7	2.3± 0.4	82
cig	16	1.0	33± 0.5	2.0	61
			33± 3.7	-	-
			30± 1.6	1.8± 0.4	60
cig	16	1.1	27± 3.0	1.7	63
cig	15	-	24± 1.1	2.7± 0.1	112
			25± 1.7	2.4± 0.4	96
cig	10	0.8	23± 2.5	1.4± 0.2	61
cig	10	0.7	27± 4.3	1.8± 0.1	67
cig	5	0.4	31± 1.6	2.1± 0.2	68
cig	5	0.4	28± 2.4	2.4± 0.2	86
cig	5	0.4	27± 1.5	2.3± 0.6	85
cig	1	0.1	21± 2.3	1.6± 0.5	76
cigar	-	-	48± 9.6	2.6± 0.6	54

* FTC Maintenance Rating [illegible].
** Non-filter cig.
*** Danish cig.
• University of Ky test cig. #1R3F

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Emission rates for RSP and nicotine for the 10 brands of cigarettes listed above, which represent 23% of the U.S. market, are 28± 3.4 mg/g and 1.9(0.3 mg/g while the corresponding nicotine to RSP ratio is 71± 10. Only the Danish and U of Ky test cigarette were removed from this calculation.

These results suggest that nicotine may be a good proxy for the single major air contaminant category associated with ETS - respirable suspended particulate matter. There are however a number of factors which still have to be examined such as whether the removal rate by surfaces in occupied spaces is the same for nicotine as for ETS related RSP. In addition, the relation of nicotine to important gas phase ETS contaminants has yet to be investigated. Work is currently underway at this laboratory to address these questions and several others.

c) Development of Air Monitoring Methods

The lack of an efficient and easy method for the collection and analysis of nicotine in air has been one of the major reasons preventing its use as a proxy for ETS. In exploring the use of nicotine as a proxy for RSP, VOCs or other air contaminants related to ETS we have developed two monitoring techniques which can be used in large scale field studies of exposures to nicotine and hence ETS. Both methods can be used either as personal monitors or as indoor space monitors.

The first method (Figure 2) is a simple, sensitive method that will collect nicotine (particulate and vapor phase) efficiently from ambient air while also collecting particulates for additional analysis (33). Two filters are assembled in tandem using a personal sampling cassette. Air is drawn through the filter system at 1.7 liters/min usi a personal monitoring pump. The first filter collects total or size fractional particulates (e.g., RSP) and the second is treated with sodium bisulfate to collect vapor phase nicotine and nicotine which has votalilized from the particulate material collected on the first filter. The nicotine is then desorbed from the filters and analyzed by gas chromatography with nitrogen sensitive detection. We have used this method in both chamber and field studies to monitor both personal exposures and concentrations in indoor spaces and it has proven to be accurate, sensitive and reliable. The major disadvantages associated with the system stem from the fact that it is an active monitoring system utilizing air pumps to collect the sample. Pumps typically cost about $1,000 each, are heavy and noisy, and present a problem in recruiting individuals to wear them for long periods of time, especially in relatively quiet areas like offices and homes. In a large field study this method would enjoy only limited use.

The finding that nicotine is predominately in the vapor phase led to our development of a passive monitor for measuring nicotine in air (2nd sampling method) (34). This passive monitor relies on diffusion of vapor phase nicotine to a sodium bisulfate treated filter, where the nicotine is absorbed. The passive sampler we have designed (Figure 3) consists of the same cassette used in active sampling, but the front part is removed and replaced with a windscreen. This gives a very large area across which diffusion can take place, and so gives a relative high effective sampling rate. The cross sectional area to length ratio of the sample is 80.

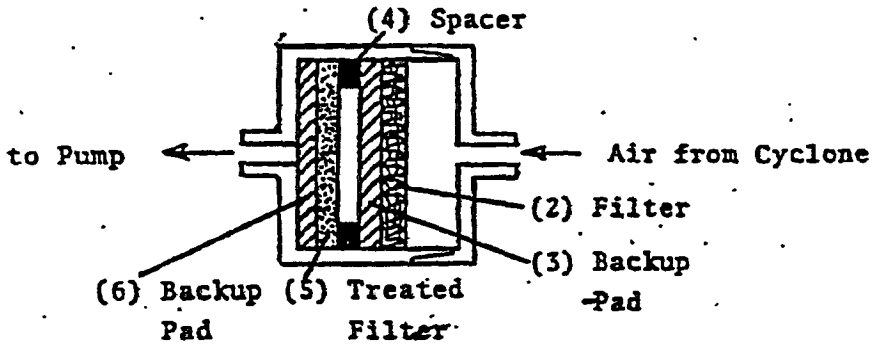

Figure 2. Diagram of the active sampling system for nicotine and respirable suspended particulates. Shown at approximately 80% of full size.

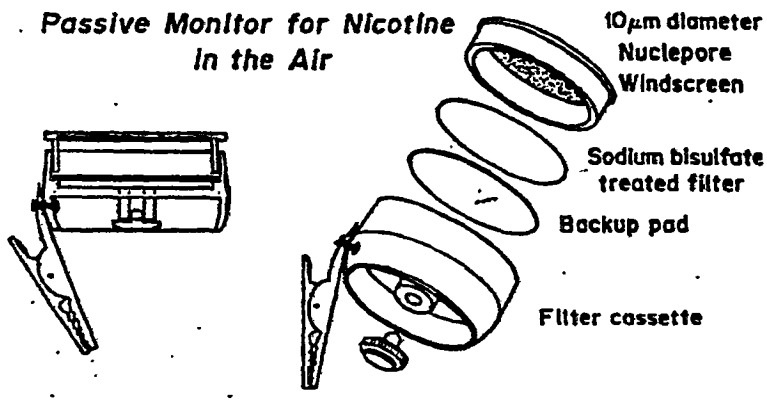

Figure 3. Diagram of the passive monitor for nicotine in air. Shown at approximately 80% of full size.

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The sampler is 37mm in diameter, 23mm in length, inexpensive to construct (approximately $5) and reusable. The sampler can be clipped to a subject's shirt lapel to place it in the person's breathing zone for personal monitoring or simply hung in an indoor space. The alligator clip makes attachment of the sampler easy and convenient. Collection occurs when the face of the cassette is uncovered; the time it is uncovered is recorded. In the laboratory, the sodium bisulfate heated filter is analyzed in the same manner as for the active monitoring system. The filter is removed from the cassette, the nicotine desorbed in water, the pH of the solution adjusted with sodium hydroxide to form the basic form of nicotine, which is then concentrated by extraction into heptane. An aliquot of heptane is then injected into a gas chromatograph and quantified with a nitrogen selective detector. The analytical method has a limit of detection of less than 0.01mg per filter.

Chamber experiments at our laboratory indicate that the passive sampler samples at a rate of 25ml/min which compares to the active sampler at 1700ml/min. The measured sampling rate agrees well with the theoretically calculated rate of 28ml/min. The sampling rate of the monitor combined with the limit of detection of the analytical method indicates that the passive monitor should easily be able to measure nicotine levels associated with low levels of environmental tobacco smoke over a 3 day or greater period. Additional chamber experiments are currently underway to further develop the passive monitor.

The passive monitors for nicotine are currently being field tested in the New York State Study of Infiltration and Indoor Air Quality being conducted by the New York State Energy Research and Development Authority (NYSERDA). The passive nicotine monitors will be used over a 7 day period in 110 of 400 participating homes in New York State. The homes have a mix of combustion sources. Data is being gathered in this study on sources and source use, building characteristics and combustion related indoor air contaminant levels. The data gathered in this study will provide an excellent field test of the passive nicotine monitor. The study was conducted during the 1985-86 heating season and the results are currently being analyzed. The results of the analysis will be available by the Fall of 1986 and be used to improve the passive samples design for use in the study proposed in this grant application.

A very limited test of the passive monitor use as a personal monitor was conducted in preparation of this grant proposal. Four subjects who reported some exposure to ETS were asked to wear the personal nisotine monitors for a one week period and to record their exposure to ETS by location (home, office, etc.), intensity (light, moderate, heavy) and time (number of hours) using a very simple diary. Table 7 shows the results of this small study

Levels of nicotine followed the reported number of total hours of exposure reported for the three subjects who reported low exposure. The one subject who reported some hours of moderate to heavy ETS exposure had levels higher than those which would be predicted by the total hours of ETS exposure alone. This data indicates that our passive monitor will be sensitive enough to measure nicotine levels that would be related to less than a 2 hour ETS exposure within a one week period.

The passive monitor for nicotine promises to be an easy, inexpensive, accurate and sensitive method of determining personal exposures to ETS or indoor space concentrations. The method is suitable for use in assessing exposures to ETS in support of epidemiologic studies.

Preliminary Studies of Maternal Marijuana Use and IUGR

Space does not permit a detailed account here of our work in this area. A detailed report is in press (36) and a copy of the manuscript attached as Appendix D.

Table 7

Personal Exposures to Nicotine from ETS Over A One-Week Period As A Function of Self-Reported Exposure

Subject	No. hours* exposed to ETS	No. hours* exposed to moderate or high ETS	Nicotine** (ug/m)
A	29	0	1.98
B	45	0	3.45
C	73	0	4.37
D	54	21	6.19

* reported by a diary questionnaire
** measured using new-passive monitor for nicotine

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D. Study Design and Methods

The study design proposed here builds upon the results of, and our experience in conducting, the Yale Pregnancy Outcome Study, and the exposure methodology and air monitoring development efforts outlined in the Preliminary Studies Section of this grant proposal.

The principal components of the proposed study are shown in Figure 4. The health outcomes of intrauterine growth retardation (IUGR), low birthweight and preterm delivery associated with exposure to environmental tobacco smoke (ETS) will be examined in a target population. The ETS exposures that we hypothesize to be associated with an increased risk of the stated health outcomes will be evaluated in a nested design involving questionnaires, air monitoring for nicotine (a proxy for ETS exposure) and the monitoring of continine (a biological marker for nicotine exposure) in marernal urine, cord blood and amniotic fluid. The nested exposure assessment builds from detailed measurements (questionnaires, indoor air monitoring, personal monitoring, urine analysis, etc.) in a purposeful sample of the study population to biochemical measures of exposure in random samples of the the whole study population (urinary cotinine), and to general measures of exposure in the entire population (initial questionnaire and telephone exposure questionnaire).

1. Target Population and Identification of Study Subjects

The target population for this study is pregnant women receiving care from private obstetricians in the New Haven area and intending to deliver at Yale New Haven Hospital during the two and one-half year study period. The following women will be excluded from the study: women who do not speak English; women who are not pregnant when contacted or who intend to terminate the pregnancy and women who are insulin dependent diabetics. The population has been restricted to women receiving care from private physicians to provide a low risk population, where the potential effects of passive smoking will not be obscured by risk of low birthweight attributable to race, low socio-economic status, and poor antenatal care. Diabetic patients will be excluded since they also have an increased risk of delivering an infant of low birthweight.

Patients will be obtained from the fifteen largest obstetrical practices with admitting priviledges at Yale-New Haven Hospital. These 15 practices currently contribute 90% of the private patients delivering infants at Yale New-Haven, annually. The physician will present the study to new patients at the first prenatal visit and record the names of women who are willing to be contacted by our reseach assistants to obtain further information. Our previous experience indicates that 4000 women will be successfully interviewed within two and one-half years, representing 85.0 per cent of eligible subjects.

Research assistants will visit physicians' offices twice weekly to obtain lists of eligible women. A research assistant will contact each woman by telephone to explain the study, to answer any questions and to

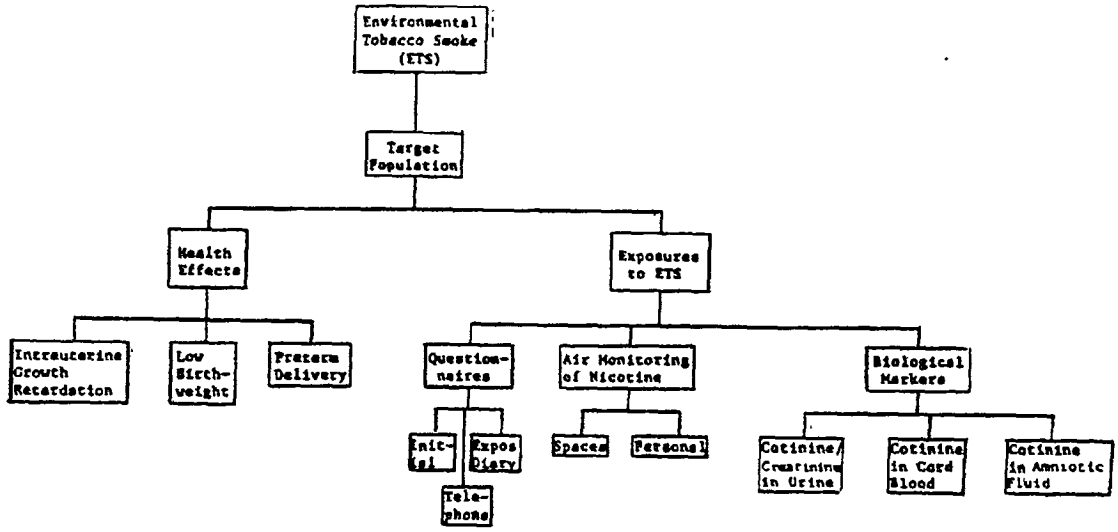

Fig. 4 Flow diagram of components of study design

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arrange an initial interview. These interviews will be conducted in the woman's home and will take place before 17 weeks gestational age from last menstrual period.

2. Interview Procedures

Initial Interview

Not attached

Research assistants will administer a standar ire with detailed questions regarding direct and passive s th prior to conception and since the beginning of the preg estions will include a complete smoking history for the y ception and the weeks of pregnancy prior to interview (Ap ons 61-66). The passive smoking questions will encomp d will ascertain exposure in the home, the workplace, com l exposures. Direct smoking will be quantified by t garettes smoked per day, while passive smoking will be quantified by the number of hours (duration) of exposure per day in each place. The intensity of exposure is assessed by the number of persons smoking in the immediate proximity, and the average number of cigarettes smoked by proximal persons, an assessment of how smoky each environment is (using a semantic differential response), and a simple question about ventilation characteristics of each environment. A preliminary set of questions about environmental smoke exposure is shown in Appendix B.

The initial interview will be used to classify women into one of four groups, women who have no exposure to tobacco smoke either by smoking themselves or passively (none); women who do not smoke, but are exposed to someone else's smoke (passive); women who smoke, but are not exposed to anyone else's smoke (direct); and women who smoke and are also exposed to smoke from others (both). This classification will be used to stratify women when randomly assigning them to monitoring using both personal monitors and urinary cotinine. Based on the preliminary study we anticipate 45% (N=1800) of the women will have no exposure, 24% (N=900) will be passively exposed, 11% (N=500) will have direct exposure only, and 21% (N=800) will have both direct and passive exposure. With more specific questions regarding passive exposure, the number of women passively exposed and those with both direct and passive exposure may increase.

In addition to the questions about tobacco smoke exposure, the initial interview will collect information about a number of other risk factors. Appendix A provides a questionnaire used by us in a recent study. The questions which will be used in the new study are referenced below.

1. Demographic data including age, race, marital status, education, religion and income. (Appendix A, Question 1 - Question 8) We will also ascertain height, current weight and pre-pregnant weight.

2. Pregnancy history: a complete record of the patient's pregnancies with dates, outcomes (whether livebirth, stillbirth, miscarriage, induced abortion or ectopic pregnancy), birthweights and gestational ages. (Appendix A, Question 33 - Question 38)

not attached

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arrange an initial interview. These interviews will be conducted in the woman's home and will take place before 17 weeks gestational age from last menstrual period.

2. Interview Procedures

Initial Interview

Research assistants will administer a standardized questionnaire with detailed questions regarding direct and passive smoke exposure both prior to conception and since the beginning of the pregnancy. These questions will include a complete smoking history for the year prior to conception and the weeks of pregnancy prior to interview (Appendix A, Questions 61-66). The passive smoking questions will encompass pregnancy and will ascertain exposure in the home, the workplace, commuting, and social exposures. Direct smoking will be quantified by the number of cigarettes smoked per day, while passive smoking will be quantified by the number of hours (duration) of exposure per day in each place. The intensity of exposure is assessed by the number of persons smoking in the immediate proximity, and the average number of cigarettes smoked by proximal persons, an assessment of how smoky each environment is (using a semantic differential response), and a simple question about ventilation characteristics of each environment. A preliminary set of questions about environmental smoke exposure is shown in Appendix B.

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1. Demographic data including age, race, marital status, education, religion and income. (Appendix A, Question 1 - Question 8) We will also ascertain height, current weight and pre-pregnant weight.

2. Pregnancy history: a complete record of the patient's pregnancies with dates, outcomes (whether livebirth, stillbirth, miscarriage, induced abortion or ectopic pregnancy), birthweights and gestational ages. (Appendix A, Question 33 - Question 38)

3. Contraceptive practice: a description of contraceptive methods used during the twelve months preceding the date of conception (and since conception if applicable) including brand names and dates of usage. (Appendix A, Question 13 - Question 32)

4. Occupational factors: each woman's job title, employer, and a description of known exposures, as well as specific questions regarding exposure to known reproductive hazards, such as lead, anesthetic gases, solvents, bacteria or viruses, and ionizing radiation. New questions will be included relating to physical stress on the job, such as standing, bending, and lifting. (Appendix A, Question 68 - Question 77)

5. Drug use: this would include any medication the woman has used whether precription or over-the-counter, during pregnancy. It also includes use of any recreational drug; marijuana, cocaine, amphetamines or others. The use of heroin and other "hard" drugs has been associated with a substantial increase in the risk for growth retardation, while the effect of drugs such as marijuana, is less well established. (Appendix A, Question 45, Question 59, Question 60). A preliminary set of questions about marijuana and other illicit drugs are shown in Appendix B.

6. Alcohol use: the consumption of beer, wine and liquor, including quantity and frequency of each since the pregnancy has begun. Alcohol is another known cause of growth retardation at high levels of use. (Appendix A, Question 46 - Question 51)

7. Caffeine: the average consumption of caffeine will be estimated, including caffeine from coffee, tea, cola, chocolate, and prescription and over-the-counter drugs. Preliminary data from our unit indicates that caffeine has a direct and dose related detrimental effect on fetal growth. (Appendix A, Question 52- Question 57)

8. Medical history: a complete history of any chronic disease with special attention to diabetes mellitus, hypertension, cardiac disease, pancreatitis (or other chronic disease interfering with digestion and nutrition); infectious diseases in the month prior to conception or since conception. (Appendix A, Question 40 - Question 44)

3. Monitoring of Exposure

In addition to the information obtained from the initial interview, both the pregnant woman and her fetus will be monitored to assess exposure to passive smoking. In the mother two methods will be used; the measurement of cotinine (a metabolite of nicotine) in urine, and a personal air monitor to measure nicotine. The personal monitor will estimate the amount of nicotine (and, by analogy, other tobacco smoke contaminants) present in the breathing zone of the woman, while the urinary cotinine will estimate the amount of nicotine actually absorbed and metabolized. Each of these measures will act as a check on the other and will be compared to the questionnaire to verify the reported exposure. Fetal exposures will be assessed by cotinine in amniotic fluid and cord blood.

Methods of Sample Collection and Analysis

Urine samples urine samples will be collected in sterilized polyethylene containers. Upon providing the sample, the study participants will be asked to refrigerate the samples until they are collected by the interviewers. The interviewer will store the samples in an ice chest in her car. Upon return to the Pierce Foundation Laboratory, 10 ml of each urine sample will be frozen at -70 C and stored for eventual shipment to the American Health Foundation for cotinine and creatinine analysis. The remaining portion of each urine sample will be frozen at -70 C for long term storage. These samples will be held for analysis at some future date for one or several biochemical markers which future research may deem indicative of either ETS exposure or some other risk factor.

Since it is not feasible to collect 24 hour urine samples, urinary concentrations of cotinine will be standardized by comparing them to creatinine excretion and expressing the results as cotinine/creatinine ratios in ng/mg. Creatinine is used to standardize the cotinine measurements since the daily output of creatinine in urine is almost constant despite variation in the output amount from person to person.

The measurement of cotinine in urine, a major metabolite of nicotine, will be done by radioimmunoassay with a modification of the method originally described by Langone et al. (37) and Hill et al. (38). This protocol uses specific antiserums produced in rabbits and has interassay and intrassay variations of 5 per cent, with a sensitivity of 0.5 ng/ml. The sensitivity of the method will be well below those levels reported for individuals reporting passive exposure to ETS (39-41). Creatinine levels in the urine samples will be determined by the method specified by Tietz (42). Creatinine in the urine is complexed with picric acid and the resulting red color is measured spectrophotometrically using an autoanalyzer. Levels of creatinine in urine samples are well above the detectable limit of the analytical method (42).

Our Laboratory has no experience in the radioimmunoassay analysis for cotinine in biological fluids while Dr. Haley from the American Health Foundation has had considerable experience and has a well established track record in this area. For this reason we will send all biological fluids to the American Health Foundation (see attached letter from Dr. Haley).

It is important to note that all samples will be collected by non-smokers in order to avoid sample contamination (e.g. nicotine containing moisture on the fingers of smokers). The samples will be handled and processed in an ETS free environment. In the case of an active smoking subject, she will be asked to take particular care not to contaminate her prime sample.

Amniotic Fluid A 2 ml. sample of amniotic fluid will be obtained from those subjects receiving amniocentesis. The sample will be stored at -20 C in small polyethylene containers and subsequently shipped to the American Health Foundation for cotinine analysis (see attached letter from Dr. Haley). Amniotic fluid samples in excess of 2 ml will be frozen at -70 C and stored for future analysis of one or several biochemical markers which future research may deem indicative of exposure to ETS or some other

risk factor. Urine samples from the subject will be collected at the time of amniocentesis and analyzed for cotinine and creatinine. The cotinine levels in the amniotic fluid will be standardized by the urinary cotinine and creatinine levels of the mother.

Cord Blood Cord blood samples (10 ml) will be obtained by the attending nurse immediately after delivery and placed in standard sterile collecting tubes where it will be allowed to clot (see attached letter from Dr. John Hobbins). Serum will be removed at the Pierce Laboratory and aliquoted into 2 ml tubes. These samples will then be stored at -70 C. A 2 ml sample will be sent to the American Health Foundation for cotinine analysis (see attached letter from Dr. Haley). The remaining sample will be stored for potential future analysis. The results will be presented in ng of cotinine per ml of serum.

Passive Monitors for Nicotine in Air The preliminary studies section of this proposal describes the newly developed passive monitor which will be used to monitor nicotine levels (ETS exposure) in occupied spaces and for personal exposures. The monitors will be constructed at the Pierce Laboratory and number coded prior to delivery in the field. Upon delivery, the monitors will be uncapped, the wind screens inserted and time of uncapping noted by the interviewer. The interviewer will place the stationary monitor in the house (room where the subject spends most of her time - exclusive of the bedroom) and/or instruct the subject on wearing of the monitor when it is used as a personal monitor. Upon return to the subjects house the following week, the interviewer will retrieve and cap the monitors recording the sampling time and the condition of the sampler.

Upon return to the Pierce Laboratory, the passive monitors will be analyzed for nicotine concentrations. The sodium bisulfate treated filters (containing the bound nicotine) are placed in centrifuge tubes containing 2 ml of water and 100 ul of ethanol and vortexed for one minute. Two ml of 10 N sodium hydroxide is added to form the free base of nicotine, and again vortexed for one minute. Nicotine is then concentrated by a liquid/liquid extraction into heptane by adding 250 ul of ammoniated heptane (gaseous ammonia is bubbled through heptane for 30 seconds) and vortexed for an additional minute. The solvents used are ammoniated to suppress adsorption of nicotine to glass walls. An aliquot of the heptane layer is removed immediately for analysis by gas chromatography. Samples are analyzed on a Shimadzu GC-7A gas chromatography equipped with a nitrogen selective detector, Shimadzu FTD-7. A Shimadzu autosampler, AOC-7, is used to inject a 3 ul of solution for each analysis. A six foot long, 1/8 inch diameter stainless steel column of Chromosorb W coated with 10% Apiezon L containing 3% KOH is used and operated isothermally at 170 C. A standard solution is run before and after each sample.

All air and biological fluid samples will be analyzed by technicians at the American Health Foundation and the Pierce Laboratory who are ignorant about any other information from the subject. A random 5% sample (blanks and duplicates) will be drawn for quality control. Some of these samples will be sent to Dr. Nicholas Wald (medical College of St. Bartholomew's Hospital, London) while a portion of the duplicate air samples will be sent to Dr. John Spengler (Harvard School of Public

Health) for analysis.

Due to the costs of collecting and analyzing these samples, not every woman and infant in the study will be monitored. When the intitial interview is complete, each woman will be designated a member of one of three study groups; the intensively monitored, the biochemically monitored, or the telephone monitored group (See figure 5). Random assignment to the latter two groups, and comparability of exposure measures among all groups will permit us to calculate weighted estimates for all exposures which represent the majority (n=3700) of the study population.

Intensive Biochemically Monitored Group (n=300)

Women who complete the intitial interview within 10 weeks from the date of their last menstrual period will be eligible to participate in the intensively monitored group. These women will be asked permission to monitor their exposure four times during pregnancy; at 12 weeks, 20 weeks, 28 weeks and 36 weeks gestation. Data from our previous study indicates that at least 500 women will be interviewed by 10 weeks gestational age, therefore we do not anticipate any problem in recruiting 300 women for the intensively monitored group. This is a purposeful sample, not directly generalizable to the majority of study subjects in the larger samples described below. This sample of study subjects will be used to provide data which examines the associations of environmental tobacco smoke as assessed by questionnaire, biochemical and air monitoring. Women who do not agree to intensive monitoring will still be eligible for either of the other two study groups.

Each time a woman is to be monitored, a research assistant will arrange to visit the woman's home. She will explain and demonstrate the use of the nicotine personal monitor. After five days, she will return to collect the personal nicotine monitor and to obtain a urine sample. At this visit, the research assistant will also ask the woman a few brief questions regarding her exposure to tobacco smoke, marijuana, alcohol and caffeine, during the previous five days. The format of these questions will follow those in the initial interview.

During one of these four visits, the research assistant will also bring a passive monitor to monitor environmental tobacco smoke (nicotine) in the home. This device will be left in the home for the five day interval and will be picked up with the personal air monitor and the urine sample. The timing of this household monitoring will be randomly determined and each of the study participants in the intensively monitored group will receive the household monitor once during pregnancy at either 12, 20, 28, or 36 weeks gestation.

At delivery, cord blood will be collected from infants whose mothers participated in the intensive monitoring. The blood will be analyzed for cotinine to enable us to compare measurements of both maternal and fetal tobacco smoke exposure. After delivery, a postpartum questionnire will be administered to every woman in the study (see below).

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR OR AWARD CANDIDATE (Last, first, middle)

BRACKEN, Michael B.

SOCIAL SECURITY NUMBER

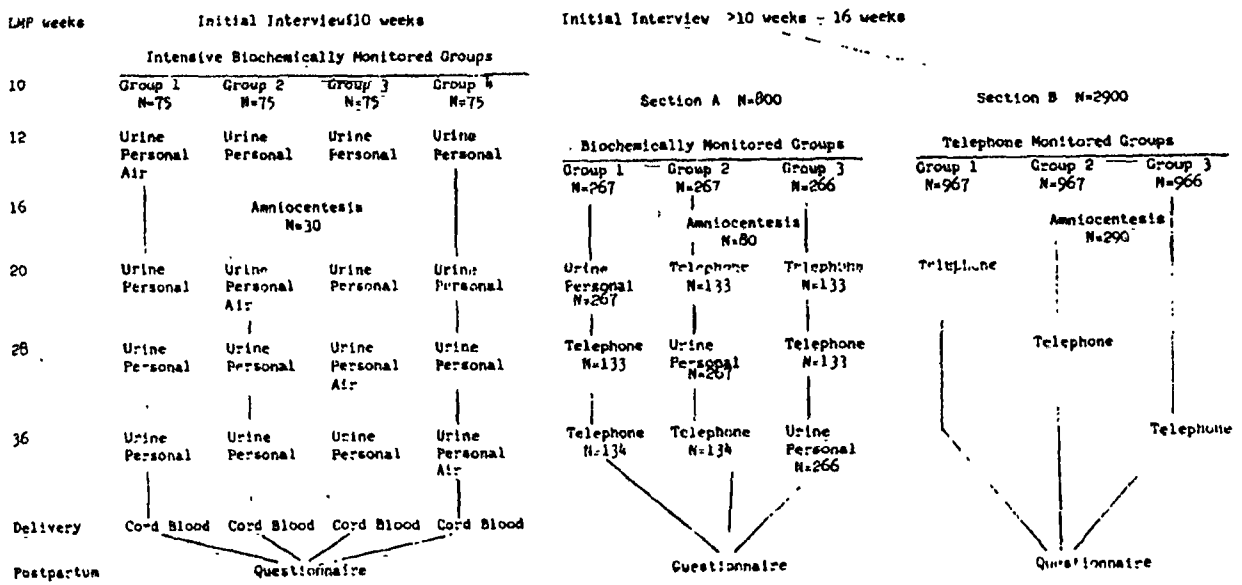

Figure 5 : Summary of data collection procedures for each sub sample.
Abbreviations: Urine = urine sample interview; Personal = personal monitor and interview;
Air = Home monitor and interview; Telephone = telephone interview only

Biochemically Monitored Group (n=800)

Women interviewed after 10 weeks, from the date of their last menstrual period, but prior to 16 weeks will be eligible for randomization in one of the other two groups; the biochemically monitored or the telephone monitored group. Eight hundred women will be randomly selected for biochemical monitoring. This will be a stratified, weighted, random sample of 200 women from each of the four cigarette smoke exposure categories; no exposure, passive exposure only, direct smoke only, or both passive and direct exposure. The purpose of this group is to provide a sufficiently large sample of women in each exposure category to reliably estimate exposure for women in the group that is not monitored.

The sampling will involve a two step process. After being randomly selected for the biochemically monitored group, each woman will be further randomly assigned to one of three sub-groups: those monitored at 20 weeks, those monitored at 28 weeks or those monitored at 36 weeks gestational age. There will be 267 women in each sub-group, one-half of the group will receive a telephone interview at each of the two time periods when they are not being monitored. For example, at 20 weeks all 267 women in sub-group 1 would have a personal air monitor for five days, a urine sample collected and a brief questionnaire. Half of these women (n=133) will be telephoned at 28 weeks, and asked the same questions. The remaining 134 women will be telephoned at 36 weeks to answer the brief questionnaire.

Telephone Monitored Group (n=2,900)

Women who completed initial interviews between 10 and 16 weeks gestational age, but were not selected for the biochemically monitored group, will be in the telephone monitored group (N=2900). These women will receive the same questionnaire as the biochemically monitored group once during pregnancy. Women will be randomly assigned to be interviewed by telephone at 20 weeks, 28 weeks and 36 weeks gestational age.

Monitoring Exposure of the Fetus (Amniocentesis and Cord Blood)

What is of fundamental interest in this study is the effect of passive smoke exposure on the fetus. Quantifying the mother's exposure is really a surrogate for estimating the exposure of the fetus. However, there may not be a direct correlation between maternal and fetal exposure. Intervening factors, such as the way smoke constituents are inhaled, metabolized, or transferred across the placenta, may effect fetal exposure. Therefore, fetal exposure will be monitored directly in amniotic fluid and cord blood.

Amniocentesis is usually performed at 16-18 weeks gestational age to detect chromosomal abnormalities or, late in pregnancy (36-40) weeks, to assess fetal lung maturity. During every subject's initial interview, a research assistant will ask each woman whether she anticipates an amniocentesis during this pregnancy. Some women may have already decided due to age (over 35) or problems in a previous pregnancy. These women will be asked to call the Perinatal Epidemiology Unit (PEU) when they know the date of the test. Reminder cards will be sent to these women at 14 weeks gestational age. Women who do not anticipate an amniocentesis, or

are unsure at the initial interview, will be asked to call the PEU if an appointment for amniocentesis is made later in pregnancy.

The PEU will notify the Genetics Clinic, Yale-New Haven Hospital when a study patient is scheduled for amniocentesis. This unit is an outpatient clinic providing ultrasound scanning, amniocentesis, and specialized services to women with high risk pregnancies, under the direction of Dr. Maurice J. Mahoney (see attached letter). A nurse from the clinic will arrange to reserve a sample of the amniotic fluid to be used for cotinine analysis. A urine specimen of the mother will also be obtained at the time of the amniocentesis, so that the maternal and fetal exposures can be directly compared for the same time period. The measurement of creatinine in the maternal urine will also be used to standardize the measurement of cotinine in the amniotic fluid.

Among women delivering at Yale-New Haven Hospital approximately 15 per cent have an amniocentesis, therefore we anticipate that 600 women in the study will have amniocentesis and at least 400 samples of amniotic fluid will be obtained. This will not, however, be a representative sample. Women who are older, who have had problems in past pregnancies, or who develop complications in this pregnancy, are more likely to have amniocentesis. However, obtaining this information is worthwhile since it is a direct measure of fetal exposure during pregnancy.

To obtain a measure of fetal exposure, all infants whose mothers are in the intensively monitored group (N=300) will have a sample of cord blood drawn at delivery (see attached letter from Dr. John Hobbins, Director of Obstetrics at Yale New Haven Medical Center). The blood will be drawn from the umbilical cord by the delivery room nurse and frozen for cotinine determination

Post Partum Interview

Each woman will have a second personal interview, conducted in the hospital during her post partum stay. This interview will not be used as a measure of tobacco smoke exposure, but to determine whether her exposure to any other risk factors for growth retardation changed during pregnancy. Changes in caffeine and alcohol consumption will be monitored by interview throughout pregnancy. The post partum interview will follow the same general format as the initial interview:

1. Occupational factors: Questions will be asked to determine whether a woman changed jobs during her pregnancy, (either within the same place of business or to another workplace) whether her job responsibilities or job exposures changed during pregnancy, and how long the woman continued to work during pregnancy.

2. Medical history: Chronic diseases that were diagnosed or became more severe after the initial interview. Particular attention will be given to pregnancy induced hypertension and preeclampsia since these conditions are often associated with growth retardation. Infectious disease contracted since the initial interview will also be of interest.

3. Drugs: Any changes in medications reported for chronic conditions, additional drugs that may have been used to treat acute conditions, or any

changes in the use or frequency of use of other illegal drugs.

Obtaining Outcome Information

To determine the outcomes of interest (low birthweight, preterm delivery and intrauterine growth retardation) it is essential to know both the birthweight of each infant and the gestational age at delivery. Preterm delivery is defined as birth before 37 weeks gestation from the first day of last menstrual period and IUGR is defined as birthweight below the tenth percentile for gestational age. Low birthweight is defined as under 2500 grams and very low birthweight as under 1500 grams when measured within 24 hours of birth. The birthweight of the infant is readily available since weight, is routinely measured and recorded for all infants. However, gestational age is much less reliably recorded. Information from the initial interview will record the date of the woman's last menstrual period. However the date is sometimes unknown or misleading in women who have irregular menstrual cycles, or women who became pregnant while using oral contraceptives. Therefore, a specially trained research assistant will use the Ballard scale to measure gestational age of each of the study infants, within 48 hours of birth. This is a shortened version of the Dubowitz scale, the definitive measure of gestational age for newborns (43). The Ballard scale contains both neurologic and morphologic items, and requires only about 5 minutes to administer. The 95% confidence limits for gestational age are ±2 weeks. When both birthweight and gestational age are known for each infant; then the number of preterm deliveries and infants with growth retardation can be determined accurately.

The following procedures will be used to [illegible]ion about pregnancy outcomes:

Ballard scale for gestational age

1. Obstetrician's offices will be reques[illegible]e Perinatal Epidemiology Unit if a study patient has a sp[illegible]on. The date, gestational age and cause of the sponta[illegible]ill be recorded. By obtaining this information from [illegible]fice, we can avoid calling women to arrange for monitoring [illegible] is no longer pregnant and may be emotionally distressed.

2. The delivery room log at Yale-New Hav[illegible]l be examined daily to identify study participants who have delivered. (Most women will be located in this way.) When the name of a study participant matches a name in the log, a research assistant will go to the hospital to conduct the post partum interview. The research assistant will also obtain the mother's consent to conduct a Ballard examination of the infant. This exam will be conducted on all healthy babies. If the infant is in the Newborn Special Care Unit (NSCU) the research assistant will not examine the infant. Since the staff of the NSCU conducts Dubowitz exams on all infants who are admitted, the Ballard information will still be available.

3. If the name of a study participant has not appeared on the delivery room log within 42 weeks of the date of the woman's last menstrual period, then her obstetrician's office will be contacted. They will be asked to check their records to determine whether the patient is still pregnant, or whether she delivered at another hospital, or moved out of the area.

Ballard
Scale
for
gestational
age

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changes in the use or frequency of use of other illegal drugs.

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The following procedures will be used to collect information about pregnancy outcomes:

1. Obstetrician's offices will be requested to notify the Perinatal Epidemiology Unit if a study patient has a spontaneous abortion. The date, gestational age and cause of the spontaneous abortion will be recorded. By obtaining this information from the doctor's office, we can avoid calling women to arrange for monitoring, when the woman is no longer pregnant and may be emotionally distressed.

2. The delivery room log at Yale-New Haven Hospital will be examined daily to identify study participants who have delivered. (Most women will be located in this way.) When the name of a study participant matches a name in the log, a research assistant will go to the hospital to conduct the post partum interview. The research assistant will also obtain the mother's consent to conduct a Ballard examination of the infant. This exam will be conducted on all healthy babies. If the infant is in the Newborn Special Care Unit (NSCU) the research assistant will not examine the infant. Since the staff of the NSCU conducts Dubowitz exams on all infants who are admitted, the Ballard information will still be available.

3. If the name of a study participant has not appeared on the delivery room log within 42 weeks of the date of the woman's last menstrual period, then her obstetrician's office will be contacted. They will be asked to check their records to determine whether the patient is still pregnant, or whether she delivered at another hospital, or moved out of the area.

Using these procedures in a recent study, the Perinatal Epidemiology Unit ascertained pregnancy outcome data on 98.2% of 4,186 women who had been interviewed during the first trimester (29).

Review of Medical Records

In addition to birthweight and gestational age, the following information will be abstracted from the mothers' and infants' hospital records: (The data collection form will be similar to one used in a previous study and included in Appendix C).

1. Factors influencing the risk of IUGR including; antepartum weight gain, number of antenatal visits, maternal weight at delivery.

2. Factors affecting the timing of delivery; planned cesarean section, premature rupture of membranes, fetal distress during labor.

3. Complications of pregnancy; maternal cardiovascular or renal disease, hypertension, gestational diabetes, nutritional disorder, vaginal bleeding during pregnancy, accident or injury during pregnancy, maternal thyroid, endocrine, genetic, neurologic, respiratory, or hematologic problems, infectious diseases during pregnancy, alcoholism or drug addiction.

4. Delivery procedures; drugs administered during labor, fetal monitoring, duration of labor, type of delivery (vaginal/cesarean), presentation (vertex/breech), use of forceps.

5. Complications of labor and delivery; abruptio placenta, placenta previa, hemorrage, prolapsed cord, pre-eclampsia, eclampsia, fetal distress, polyhydramnios, oligohydramnios, post partum hemorrhage, obstetrical trauma.

6. Infant assessment; sex, birthweight, length, head circumference, Ballard assessment of gestational age, Apgar scores at 1 minute and 5 minutes, record of all major and minor anomalies, resuscitation or ventilation, placement in special care nursery.

7. For infants placed in special care nursery; length of stay, discharge diagnoses, date of death and autopsy results (if applicable).

Data Analysis

Data collected from the "Intensive biochemically monitored group" and the "Biochemically monitored group" will be analyzed to determine the association among measures of passive smoking. Linear models will be used to empirically derive equations which predict nicotine exposure, and urinary cotinine. This analysis will first explore the relationship between variables using graphical methods, such as scatter plots, progressing to multiple regression and the adjustment of covariates. At each step the model assumptions will be considered, and if the usual assumptions of multiple regression analysis are not realized, a more realistic model will be derived.

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The usual regression model has the form

$$Y = b_0 + X_1 b_1 + X_2 b_2 + \ldots + e$$

Where Y is the response, the X's are regressor variables, the b's are regression parameters, and e is random error with some specified distribution. When measuring the associations among the estimates of tobacco smoke exposure several regression models will be explored. First the levels measured by the personal monitors will be regressed on information from the questionnaire. Similarly, urinary cotinine will be regressed on the level of exposure recorded by the personal monitors as well as information from the questionnaire. The strength of the association will be indicated by the R-square statistic. It will also be necessary to explore the effects of these factors by themselves as well as in combination with other factors, including how far along in pregnancy the measurement was obtained, demographic information, alcohol use, caffeine use, and drug use. These factors may have an additive affect on the response, but it is also possible that they modify the association between X and Y. To investigate this possibility, interaction terms will be evaluated.

In the case of the "Intensive Biochemically Monitored Group," each patient is evaluated at multiple points in time. These "repeated measures" will be incorporated in the analysis using a repeated measures analysis of variance, and methods for the analysis of random-effects in longitudinal data (44-46).

Data from all the groups will be combined to estimate the health effects of passive smoking on infants. This analysis will estimate the association between exposure to passive smoke and delivering an infant with low birthweight, or before 37 weeks gestation, and/or with intrauterine growth retardation. The models for this analysis also have the form given in equation (1). In these cases the response is binary, so that Y represents a transformation of the probability of a given response, such as the probability that the infant has low birthweight. The usual transformation is the logit transformation; however, with the statistical package GLIM (47), it is possible to explore other models, as well. From this analysis estimates for the relative risk and corresponding confidence intervals for passive smoke exposure will be obtained, as well as estimates of the dose response relationship. These estimates will be obtained both adjusted and unadjusted, for other covariates. This analysis will also explore interaction terms, so that it can be determined whether certain subgroups are at especially high risk.

Of special interest is the month during pregnancy at which the exposure takes place. This study has been designed so that smoking exposure is measured at various times during the pregnancy. For example, to determine the association with exposure at 20 weeks, data from all three subgroups will be combined for those patients which were interviewed at 20 weeks. In a similar way the associations at the other times will be estimated. This will enable us to determine whether the association is especially strong at one point in time. However, it is quite possible that passive smoking exposure changes very little during pregnancy, so that there is a high correlation in the measure at the different points in time. If this is the case, it may be impossible to separate out the

differences over time, and a single estimate of passive smoking will be obtained. For this estimate all of the data will be combined in a single final analysis.

Sample Size and Power Estimates

During the two and one-half year data collection period, 4,000 women will participate in this study. Data from the Yale Pregnancy Outcome Study (29) indicates that 45 per cent (n=1800) of the women will have no exposure to direct or passive smoke, 24 per cent (n=900) will be passively exposed, 11 per cent (n=500) will have direct exposure only and 21 per cent (n=800) will have both direct and passive exposure. These estimates have been used to calculate sample size for the proposed study, although with improved exposure assessment methods, the proportion of women passively exposed and those with both passive and direct exposure is expected to increase.

Data from the Yale Pregnancy Outcome Study has also been used to estimate the incidence of the perinatal outcomes of interest. Among private patients delivering at Yale New Haven Hospital, 4 per cent delivered a liveborn infant weighing less than 2500 grams. Growth retardation is defined as the lowest tenth centile of weight for gestational age. Since the tables of weight for gestational age have often been constructed using higher risk populations than the one to be used in this study, a conservative estimate of IUGR in a low risk population is 5 percent.

The proposed study will include four exposure categories; no exposure, passive exposure only, direct exposure only and both passive and direct exposure. Each of these categories will be of importance in testing specific study hypotheses, however to calulate sample size only the women with no exposure and those with passive exposure only have been considered in the power calculations.

Table 8 demonstrates the sample sizes and statistical power (1-B) necessary in the proposed study. For example, to examine the effect of passive smoking on low birthweight, 899 women who are passively exposed to tobacco smoke during pregnancy compared to 1798 women with no exposure (passive or direct) would offer 95 per cent probability of detecting a two-fold increase in risk of low birthweight. Similarly, if exposure to passive smoke during pregnancy doubled the risk of IUGR, 730 exposed women and 1461 unexposed women would be needed to obtain 95 per cent probability of detecting this effect. Thus, the anticipated number of passively exposed women (n=900) and unexposed women (n=1800) would have 95 per cent probability of detecting a doubling of risk for either of these outcomes. Furthermore, some analyses will use birthweight and gestational age as continuous variables, this will further increase the power in these analyses.

Table 8

Statistical Power and Sample Size Estimates for Selected Perinatal Outcomes

Incidence in unexposed group	Number of pregnancies with no exposure	Number of pregnancies with passive exposure only	Statistical Power[1] (1-β)
.04	1170	575	.80
	1488	744	.90
	1798	899	.95
.05	912	466	.80
	1208	604	.90
	1461	730	.95

1. α = .05, odds ratio 2.0

4. Field Operations (Data Collection and Data Management)

Data Collection (Figure 7)

The study will be conducted from the Perinatal Epidemiology Unit which was established in 1979 and from which several studies of similar structure have been conducted. The Unit will be the base for staff training, data collection scheduling and assignments, supervision of field staff, and data management. Six part-time research assistants will be trained to begin interviewing in year one. The training will involve readings, discussion, films and role-playing. Interviewers will be blind to the specific study aims.

The project coordinator will provide participating physicians with copies of a study information sheet to be presented to all new obstetric patients. The coordinator will obtain initial patient lists from the doctors' offices. An introductory letter will be mailed to each potential subject notifying her that a research assistant will call to answer questions and schedule an interview if she chooses to participate. Assignment cards will be typed simultaneously with the letters and the coordinator will distribute the assignments to the interviewers by geographic region to maximize the efficiency of field contacts.

Interviewers will be responsible for contacting potential subjects and arranging interviews as soon as possible. Women who cannot be interviewed prior to 16 weeks from the date of their last menstrual period will not be included in the study. Daily, following their interviews, research assistants will transcribe smoking and amniocentesis information to a cover sheet for immediate data entry and monitoring group assignment. The balance of the interview will be coded and cross checked within a week of its completion and submitted for data entry.

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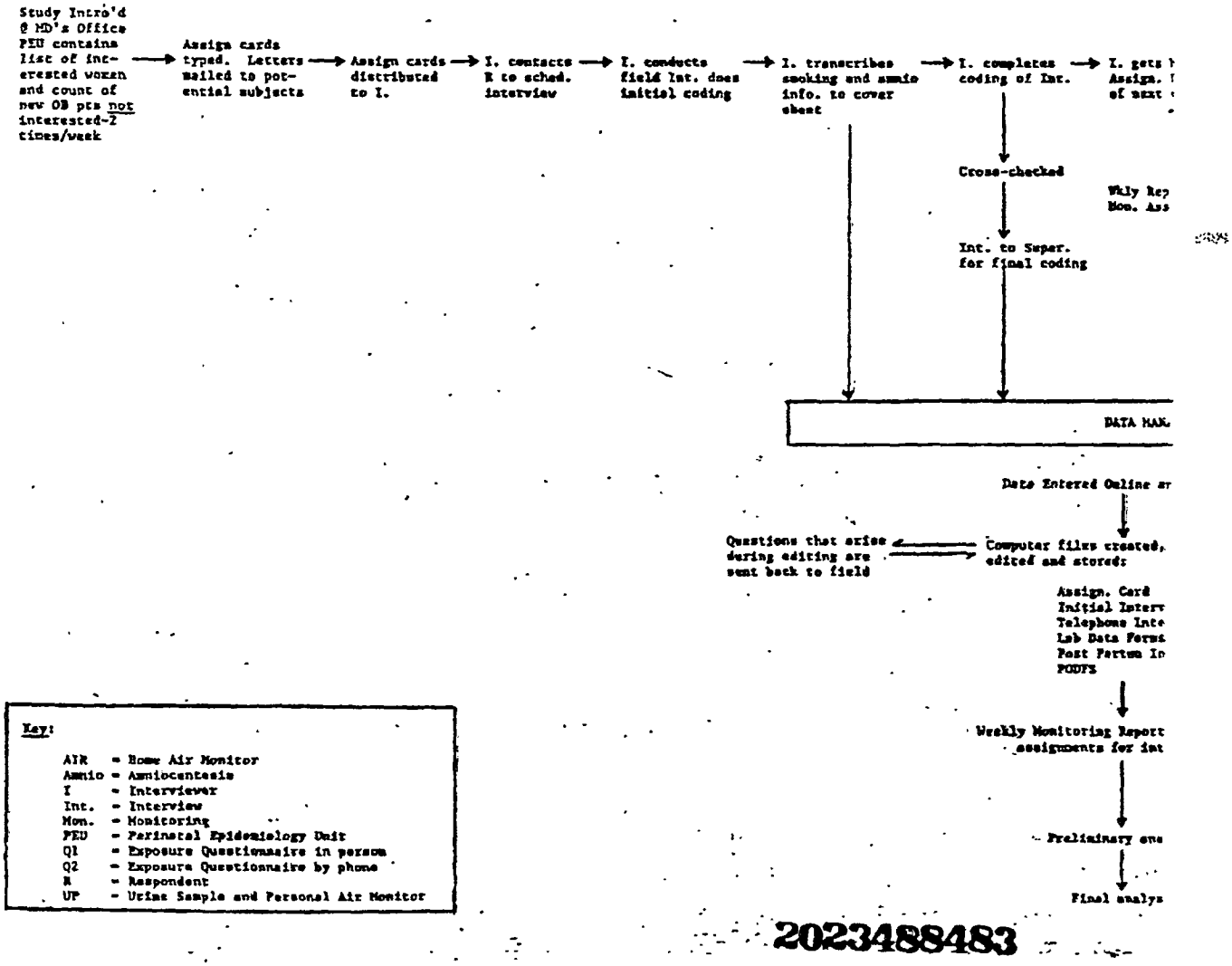

Key:

AIR	= Home Air Monitor
Amnio	= Amniocentesis
I	= Interviewer
Int.	= Interview
Mon.	= Monitoring
PED	= Perinatal Epidemiology Unit
Q1	= Exposure Questionnaire in person
Q2	= Exposure Questionnaire by phone
R	= Respondent
UP	= Urine Sample and Personal Air Monitor

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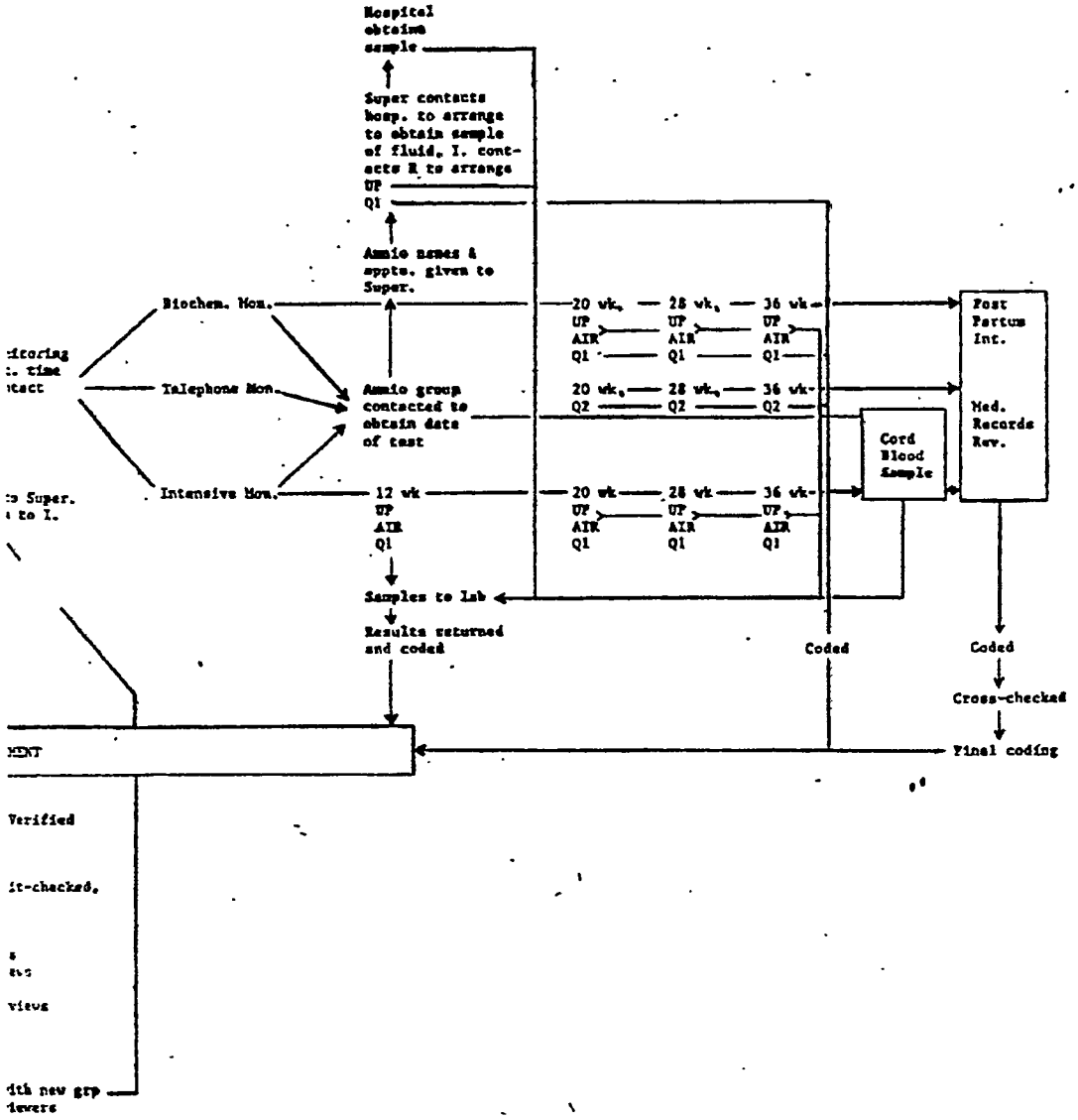

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The data manager will produce a weekly report with group assignments from which monitoring assignments will be made by the coordinator. The interviewer who conducts the initial interview with a subject will be responsible for her follow-up monitoring.

By week 27 of data collection each interviewer will be responsible each week for: 5.5 interviews, 2.7 biochemical monitorings, .54 amniocentesis contacts and follow-up and 5 telephone questionnaires. Interviewers will be responsible for promptly returning urine samples and air monitors to the field office for transport to the Pierce Laboratory. Laboratory results will be recorded on data forms and returned to the field office for data entry.

Additional research assistants will be hired to begin post partum interviews and review medical records in week 31 of the study. The research assistant who reviews the medical records for a specific woman, will not be the same person who conducted the initial interview, telephone interview or monitoring for that woman. This is to insure that the individual abstracting outcome data from medical records will be blind to the exposure status of the subjects.

All study data will be entered on-line and files will be created, error checked and edited on a continual basis throughout the data collection phase of the study. To insure that the entering of data and monitoring of women during pregnancy does not get behind schedule, two four-week time periods during which no new subjects will be enrolled, have been built into the data collection schedule. The first will occur during December of year 2 and the second during December of year 3. These months have been selected to coincide with the holiday period when it would be difficult to schedule initial interviews. These "catch-up" periods are expected to minimize the amount of clean-up required at the end of data collection and to allow analysis to proceed on schedule.

Data Management

Once the data has been collected, coded and checked by the field staff it will be turned over to the data management staff for computer processing. The data will consist of 5,000 screening cards, 4,000 initial interviews, 2,000 urine analyses, 2,000 analyses of personal nicotine monitors, 300 analyses of household nicotine monitors, 6,100 telephone questionnaires, 4,000 postpartum questionnaires and 4,000 medical record review forms (Figure 6). To keep computer costs minimal both the Yale University mainframe and two IBM personal computers will be used. The longer forms, initial interviews, post partum questionnaires and medical record review forms will be processed on the mainframe whereas the remaining shorter forms will be processed on the personal computers. This is due to the inherent memory and software restrictions that are present on the personal computers. Data file creations, editing and reporting will take place on the IBM AT, at the same time as data is being entered on the IBM XT. The Statistical Analysis System (SAS) will be used for all data file creations and editing as will as producing weekly reports and performing statistical analyses. By using SAS for both the mainframe and personal computers minimal file reformatting and changes will be necessary for combine information processed on the mainframe and personal computers for cross file checking and analyses.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR OR AWARD CANDIDATE (Last, first, middle)

BRACKEN, Michael B.

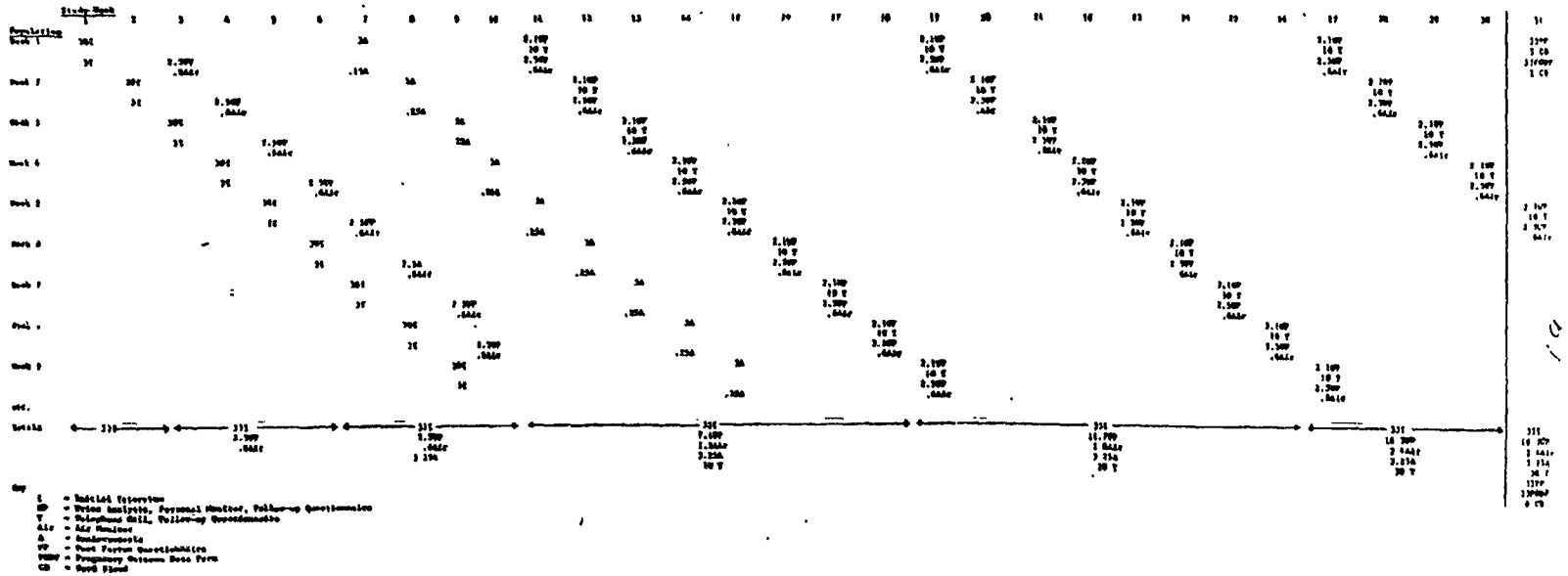

Figure 6 : Calculation of data elements being collected during each study week

In a study of this design, where respondents will be monitored over an extended period of time, it is important that a large proportion of the computer programming be completed prior to the collection of data. This will ensure that once the data collection begins, data can be processed efficiently.

The data will be processed in the following manner:

1. All data will be entered online and verified by a full time data entry person on a weekly basis.
2. The weekly raw data files will then be read into a SAS file and error checked. The error checking will consist of checking for out of range values, and inconsistent responses.
3. When the errors have been corrected, the weekly files will be concatenated into a "clean" master file.
4. The master files will be used to produce weekly reports.

By processing the data in small amounts the data flow can be kept more manageable. It is important to note that since the screening cards will contain the information necessary to categorize respondents by exposure for execution of the sampling design they will be processed first. The master screening card SAS file will contain all the necessary information to produce a weekly report that will summarize the study's overall current status (numbers, response rates, etc.) as well as give a listing of respondents who need to be monitored in the following 3 weeks. This will be a necessity for the field staff to make certain that monitoring is executed correctly and on time. By giving the processing of the screening cards the highest priority, any unforseen delays will not effect the successful execution of the study.

I. Human Subjects

Subjects will be patients anticipating delivery at Yale-New Haven Hospital and seeking their antenatal care at private medical groups. The study will be initially introduced to the women by their medical practitioner. After they have agreed to be contacted our study staff will seek their formal approval to participate. The research assistant will describe the study and seek oral consent. If we need to obtain additional information from health care providers we will obtain written release. The only potential risks to the subjects will be from questions asking them about illicit drug use. A certificate of confidentiality will be obtained for the study and all our data will be kept in locked storage. No benefits will accrue to the subject from this study. Documentation of risks to the fetus from environmental tobacco smoke, illicit drug use and other risk factors will have important social implications.

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